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ABSTRACT

The discussion of genetic and environmental factors in the growth of children from infancy to adolescence focuses on intrauterine life, the effects of nutrition, hormones, illness, and emotion in the childhood years, and obesity and puberty in adolescents. Described are processes, such as amniocentesis, for monitoring the physiology chemistry of the uterine environment. The neonate suffering from intrauterine growth retardation is distinguished from the premature infant, and risks of each are specified. Noted are variant growth patterns in males and females such as the much lower production of muscle cells in the female. It is said that radioimmunoassay has revolutionized the chemical analysis of hormones such as human growth hormone, insulin, and thyrotrophin whose functions are explained. Also analyzed are the effects on growth and development of emotional deprivation and of illnesses such as malnutrition, sickle cell anemia, and heart disease. Treated are the physiological processes underlying growth spurts of puberty, which are said to make puberty the most difficult time in life to lose weight. (GW)

ED 069058

Clinical Research Advances in Human Growth and Development

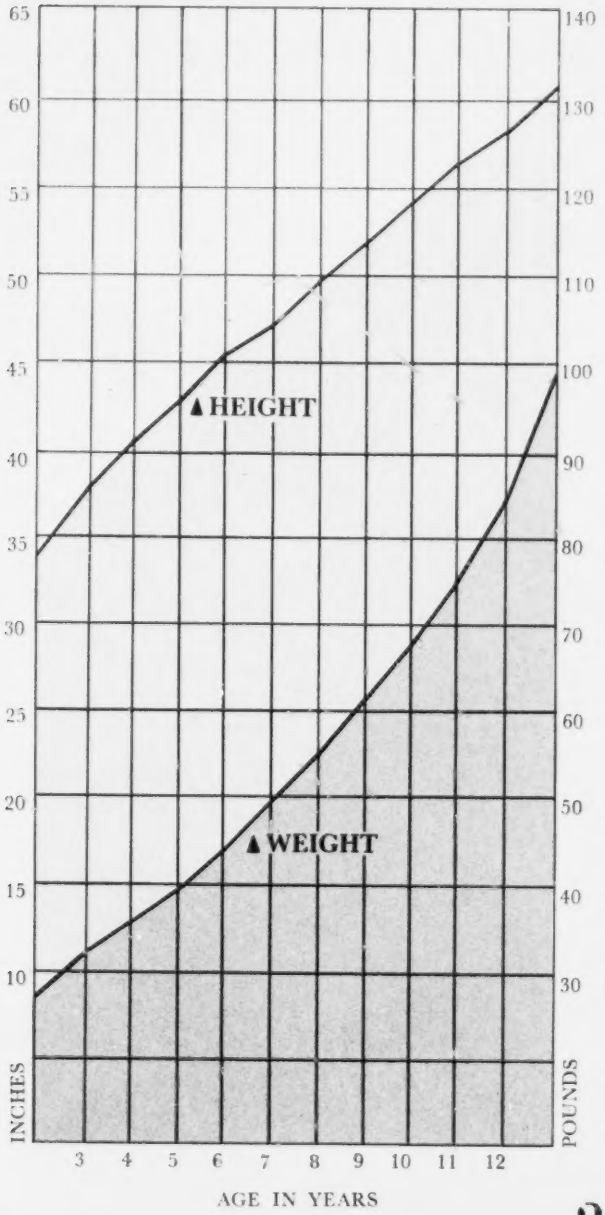
How Children Grow

EC 050 108E

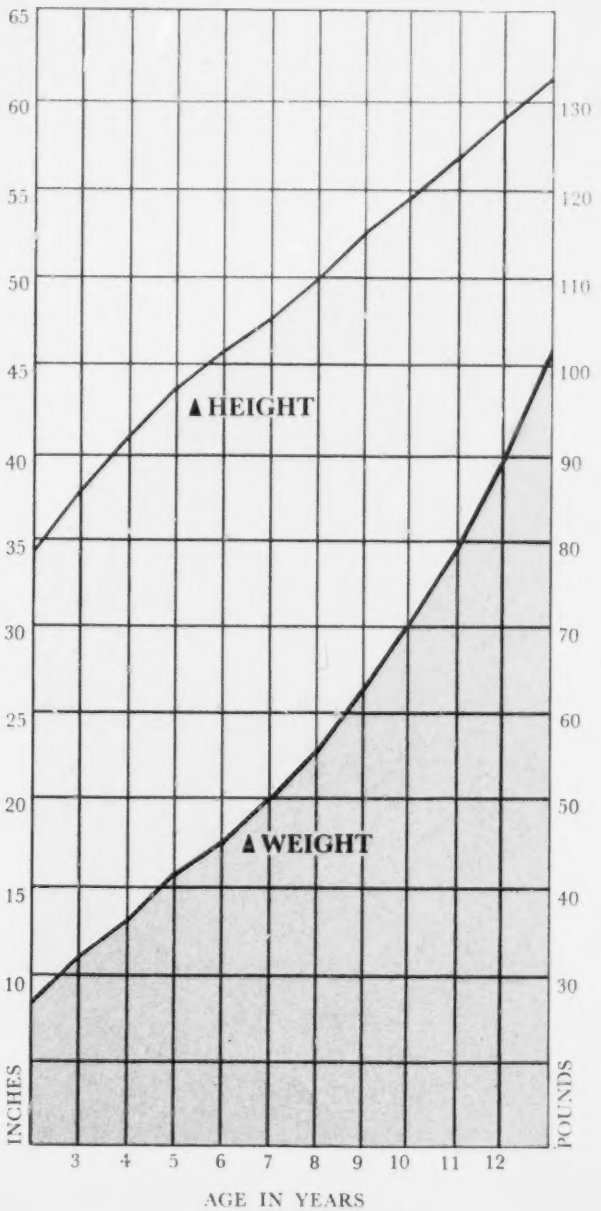
Average Physical Measurements

Black lines indicate 50 percentile.

Boys (2 yrs. or older)



Girls (2 yrs. or older)



How Children Grow

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Introduction

The mature human body is the end result of a remarkable growth process that requires almost two decades for completion. During this 20-year period, the individual who initially was the product of two germ cells, becomes an adult made up of 100,000 billion cells. Yet, contrary to popular belief, size increase is perhaps the least significant of the many components of human growth.

The human being at any age is very complex: he represents a marvel of specialized tissues and complementary functions—all coordinated to allow continuing integrity of his body as a whole. Fundamental to the growth process is the fact that all body systems must continue to work in concert at every stage of growth. Changes must be timed with exquisite precision, not only to culminate in a unified adult, but also to insure the integration of body activities which is essential at each intermediate point in growth. For this highly complicated process to evolve normally, physiologic systems must come into being in nicely ordered sequence, and they must be synchronized with others already in existence or yet to come. This is why the study of growth at its most basic levels may be viewed as an approach to better understanding of the nature of life itself.

Research in any branch of medicine is usually first conducted at the basic science level using laboratory animals. For growth research, rats are most commonly used since even after maturation they can be induced to grow almost at will. Growth research advances are next tested in primates (apes and monkeys) because their physiologic systems most closely parallel those of man. Finally, growth is studied in human volunteers, whose normal or disordered growth processes ultimately are not duplicated in any other living creature.

For the past decade, much of the clinical research in the United States on the complex process of growth in humans has been conducted in General Clinical Research Centers supported in medical institutions across the Nation by the Division of Research Resources of the National Institutes of Health. The General Clinical Research Centers program currently funds 80 research centers in 70 of the Nation's research institutions and medical schools. Within the program as a whole, there are 742 adult and 163 pediatric research beds plus a manpower force of over 2,000 physicians and other specialized medical personnel.

Each clinical research center is a "hospital in miniature," a medical ward specifically designed for research in human health. Generally located in a university hospital, the "average" center consists of 11 research beds, a director's laboratory, two research laboratories, a metabolic kitchen, a procedure room, and a treatment room.

A patient is admitted to a research center only as part of a precisely defined research protocol, and his hospital stay is constantly supervised by a physician-investigator. The details and aims of the study, as well as the risks, if any, have always been carefully explained to the patient. The study has also been reviewed and approved in advance by an appointed group of independent hospital physicians.

In its 10-year history, the General Clinical Research Centers program of the National Institutes of Health has contributed more than $68 million in Federal funds to clinical research on human growth. Center investigators have used over 518,000 bed-days to study growth processes. This represents research on an average of 142 inpatients *each day* for the past 10 years.

Within a recent 1-year period, over 1,500 separate studies on human growth were conducted in General Clinical Research Centers. More than one-third of these projects concentrated on the influence of hormones on growth. (Hormones are the major chemical determinants of when growth begins, how it proceeds, and when it stops.) Other projects sought to define the effects on growth of such diverse influences as prenatal life, heredity, nutrition, illness, and even sex and emotion.

Medical scientists study periods of intense growth with unusual interest. In addition to providing ideal conditions for the basic study of growth and its derangements, these periods also represent a natural laboratory where solutions may be sought to many of the serious, nongrowth-related disorders that plague people throughout life.

For example, cells multiply at their greatest rate between the time of conception and the beginning of puberty. This period—the fetal and childhood years—is perfectly suited for research into the control of human cell multiplication. Through such research, physicians may in time learn why, in many people, abnormal cell division produces cells that, unfortunately, are not carbon copies of the originals, and why cellular growth in some people becomes completely uncontrolled or cancerous.

As the difference in growth between boys and girls becomes more fully documented, General Clinical Research Center investigators may also define those influences—both genetic and environmental—responsible for the greater longevity enjoyed by women in all developed nations of the world.

Also, growth studies will undoubtedly result in significant discoveries about the disabilities of old age, particularly those due to unstable cellular changes and to the diminishing ability of the body to repair itself. In time, physicians may even be able to circumvent many of these infirmities.

As we have seen, clinical studies on human growth have application, directly or indirectly, to many of the medical problems experienced by people of both sexes and of all ages. Today, medical research at the basic science and laboratory levels is being quickly translated into improved medical care for all people with the help of investigators studying these and other health mysteries in the General Clinical Research Centers of the Division of Research Resources, National Institutes of Health.

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Intrauterine Life

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***The most rapid and crucial period of growth in** the human being occurs in the 9 months before birth. Because this growth takes place within the cloistered setting of the uterus, it has not been in the past readily available for study. However, this historic lack of knowledge is being rapidly overcome as clinical investigators join with basic scientists in the development of new research techniques to study fetal growth during pregnancy. The availability of these new techniques has improved obstetrical care strikingly within the past 5 years. Many of the disorders that cause breakdowns in the normal chain of events of pregnancy can now be either detected early and treated, or circumvented.*

Scientists have known for years that, except for the sperm and ova (the reproductive cells produced by the male and female), the billions of cells in a single human body all share identical genes—blueprints inherited from the parents that determine how the body is to be constructed. These genes, themselves composed of specific sequences of chemical substances, are normally linked end-to-end in precise order to form long thin strands. Within the nucleus of each body cell, the strands exist in segregated, complementary pairs, the two strands intimately associated in a spirally entwined configuration. This double-stranded coil constitutes one "molecule" of deoxyribonucleic acid (DNA), which, in association with the other DNA molecules in the nucleus, controls chemically every activity of the cell in which it exists.

When an ovum or a sperm is formed, the two strands of each molecule of DNA uncoil and separate, and only one of each pair is donated to the germ cell. At conception, with the union of ovum and sperm to form one cell, single complementary strands from each of the two parents unite to form a new paired DNA spiral, which will then be duplicated precisely in each body cell of the new human. In this way, both parents contribute equally to the chemistry of life passed down from one generation to the next.

The first 2 weeks of pregnancy is the period in which the newly conceived life fastens itself to the uterine wall. This union starts the enlargement of the uterus and begins the development of the placenta—the organ by which the unborn baby is attached to the wall of the uterus and on which he will depend throughout the pregnancy for nutrition, respiration, and excretion.

At various times during the ensuing pregnancy, the genes trigger or suppress the production of enzymes—organic catalysts that determine how fast or how slowly specific chemical reactions occur within the body. These reactions, in turn, determine whether and when a developing cell will become part of specialized tissue such as heart, lung, bone, muscle, or fat.

The uterus provides the requisite environment for different organ systems to develop harmoniously. Much evidence is accumulating that the uterine environment may wield as great an influence as does genetic endowment in determining how large the fetus may grow before birth.

Between the 2d and 10th weeks of pregnancy, the cells for arms and legs, eyes and ears, and vital organs are differentiated. This is now proven to be a most vulnerable period of life. Many severe birth defects have been traced by researchers to maldevelopment during this phase of prenatal growth.

Today, scientists have new, reliable bioengineering tools for monitoring the physiology and chemistry of the uterine environment, and they can identify very early some of the genetic makeup of the fetus. For example, the process of amniocentesis, developed at a General Clinical Research Center, allows a doctor to safely withdraw, through the mother's abdomen, some of the fluid in which the fetus is bathed. From analysis of the fluid, physicians can detect within the early months of pregnancy whether certain birth defects are developing in the fetus. The test was developed as a research technique, but it is now widely used clinically as a diagnostic procedure.

Development of the skeleton begins in the 2d month of intrauterine life. Almost all bone in the body is first laid down in the fetus in the form of *cartilage*—a flexible material which persists in adulthood in such areas as the ears and nose. *Ossification,* the process by which cartilage is replaced by true bone, however, only *begins* in fetal life. It continues throughout childhood and is not concluded until the end of puberty.

The initial sign of impending ossification in a specific area of cartilage is the swelling up and arrangement of the cells into ordered columns. These cartilage cells then disintegrate, and as they break down, a protein matrix—the basic material of the subsequent bone—grows into the space they vacate. This matrix in turn absorbs minerals, such as calcium and phosphorus, from the blood stream and thereby attains the composition of true bone. Those areas in which the conversion of cartilage begins are known as *primary centers of ossification.* They, unlike cartilage, show up on X-ray.

As the process continues, different areas of ossification within a potential bone grow toward one another until a stage is reached in which a thin disc of cartilage is all that remains between two areas of bone. This disc continues actively to grow on one surface while its conversion to bone proceeds concomitantly on the other, resulting in steady growth in length of the bone. The most common examples of such linear growth are in the long bones of the arms and legs, in which, simplistically, a growing disc of cartilage at either end continues to proliferate throughout childhood. These plates of actively growing cartilage between two areas of bone are known as *epiphyses.* At the end of puberty, in the process known as *epiphyseal closure,* the cartilaginous plates are completely converted to bone, and no growth of the bone subsequently can occur.

As bones increase in length, so must they also increase in width. This requires the deposition of new bone on the external surface of the shaft and, simultaneously, an absorption of old bone from the center. The result is mature bones having roughly the configuration of a hollow pipe, the center cavity of which becomes filled with bone marrow, from which cells of the blood are eventually produced.

Radioisotope studies have revealed that once bone is formed, it does not remain inactive. Throughout life, it is constantly being destroyed and re-formed as minerals such as calcium and phosphorous are exchanged between bone cells and body fluids. This bidirectional flow enables bone to serve as a reservoir of minerals needed, on demand, by other body systems. In the growing fetus and child, of course, bone mineralization exceeds demineralization, permitting the skeleton to grow in size and strength.

The latter months of pregnancy are devoted primarily to further development of existent body organs and systems. By the 6th month, fatty tissue starts to build up; at every stage of pre- and postnatal growth, its main function will be to store energy and help regulate body temperature. During the last 2 months, the fetus grows so rapidly that it gains about one-half pound a week.

At one General Clinical Research Center, amniotic fluids, blood pigments, waste products, and fetal cells are analyzed during the last months of pregnancy to determine more accurately the changes that normally occur during this time of rapid fetal growth. This and other newly developed ways to examine fetal growth reveal again the remarkably favorable intrauterine environment usually provided by the pregnant woman. In addition to the physical protection it affords the growing fetus, this environment is admirably designed to promote between mother and child the steady, dynamic exchange of substances required for optimal fetal growth.

Indeed, so long as the flow of blood to the uterus is normal, and the concentration of nutrients traveling through the placenta is adequate, the fetus will probably grow to be at least 5½ pounds at birth—the dividing line between the normal and the low birth weight newborn.

Low Birth Weight Babies

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Many General Clinical Research Centers are conducting intensive studies of infants who fail to grow to normal size before birth. By focusing on the unique problems of these low birth weight babies, scientists may be able to halve the infant death rate in this country and, perhaps, eliminate the major cause of brain damage in children. As the mysteries of prenatal growth are examined more intimately, increasingly sophisticated techniques of obstetrical care will likely be developed. And these new techniques may in time enable more and more mothers to provide their unborn children with the uterine environment most conducive to healthy growth.

The size of a new baby is closely linked with the size of the placenta. This consistent correlation has been part of midwife lore for centuries. Large infants always have large placentas. Twins, triplets, and other multiple births have even larger placentas. Scientists, therefore, suspect that the upper limit in size that a fetus can attain is directly dependent on the amount of placental tissue adequately conveying nutrients and oxygen to him.

Small babies usually have small placentas. Sometimes a small baby has a large placenta, but in such a case, a portion of the placental tissue may have been defective and functioning improperly.

Several scientists have found that, during a normal pregnancy, the adrenal glands of the fetus work in concert with the placenta to manufacture hormones that dilate the arteries which supply blood to the uterus. This allows the increased blood supply required by the growing fetus. This metabolic interplay between the placenta and the fetal adrenal glands is mediated by the hormone estriol. The measurement of this hormone in the urine of the mother is one of the newest methods an obstetrician can use to determine if placental development is proceeding normally. A relationship also exists among a low excretion of estriol during pregnancy, a constricted blood supply to the uterus, and subsequent low birth weight of the baby. Having established this relationship, researchers are seeking ways to enable the physician to increase blood flow to the uterus in an attempt to avert the delivery of a low birth weight baby.

Although human growth hormone (HGH) has been identified in fetal blood as early as 15 weeks after conception, to this day no evidence exists that HGH regulates the size of the fetus. Considerable progress has been made in isolating human placental lactogen, an HGH-like material present in the placenta; yet, studies indicate this hormone probably does not reach the fetus in amounts sufficient to control his growth.

Infant survival rate is inversely correlated with birth weight; the lower the weight of the newborn, the greater the danger he faces. Until recently, all infants weighing less than 5½ lbs. at birth were automatically classified as "premature," and their postnatal conditions were evaluated and treated according to the same guidelines of care. However, physicians are recognizing increasingly that intrauterine growth retardation, not prematurity, may account for one-third to one-half of all low weight newborns. The distinction is of paramount importance in that postnatal care appropriate for the true premature, born before completing 36 weeks of intrauterine life, may be inappropriate, or even contraindicated, for the low birth weight infant who has gone full term.

Early pregnancy is the most propitious time to determine if growth-retarded development is taking place. The sooner the suspicion can be confirmed, the more effective are the steps that can be taken to ward off, or diminish, the problems of the affected infant. However, traditional ways of estimating whether a fetus is growing normally, based on a comparison of probable duration of pregnancy with clinically estimated weight of the fetus, are often little more than educated guesses. A new method to allow physicians to accurately gage fetal size uses an ultrasonic sound device, developed in a General Clinical Research Center, which yields a three-dimensional "map" of the unborn child. In addition, amniocentesis allows a very precise measure of the duration of the pregnancy. A combination of these tests enables a physician to determine precisely whether a fetus is of a size appropriate to his age.

If prenatal tests were not conducted, or were inconclusive, clinical methods are available to distinguish at the time of birth the intrauterine growth-retarded newborn from the true premature. Charts relating the age at which various neuromuscular reflexes develop have been prepared by one clinical research center and are now present in most delivery rooms and nurseries in this country. The true age of a given small newborn is determined as the age of his typical neurological behavior.

The growth-retarded newborn is expected to exhibit the same patterns of behavior as any other full-term infant; the premature infant, on the other hand, should display patterns consistent with neurological functions which are not completely developed and may yet evolve.

The mature behavior of the growth-retarded infant, as opposed to that of the premature, can be quite striking. Many premature infants, for example, have poor sucking and swallowing reflexes; fortunately, scientific advances at one General Clinical Research Center permit such an infant to be fed through tubes inserted through the abdominal wall into the stomach, a procedure that has proved sufficient for adequate nutrition. This support is often not needed by growth-retarded infants. Instead, many of these infants weighing less than 3 pounds can be observed vigorously enjoying nipple feeding in their incubators.

One major complication to be anticipated for the newborn suffering *intrauterine growth retardation* is a pathologically low blood sugar level, known as hypoglycemia. In the normal sized, full-term infant, large stores of glycogen, a storage form of sugar, are present in the liver. This reserve enables the infant to maintain normal blood sugar levels for relatively long periods after birth. The newborn with intrauterine growth retardation, however, has markedly depleted his glycogen stores during pregnancy and stands a great risk of developing, soon after birth, such low blood sugar levels that severe brain damage may result. Prompt injection of glucose, therefore, is becoming a common procedure in newborns identified as growth-retarded.

The greatest danger faced by the *premature* baby is a respiratory condition known as hyaline membrane disease. Marked by progressive collapse of the thin air sacs which make up the lung, the ailment causes the lungs to lose their power to expand. As the lungs become increasingly resistant to the entry of air, they render the premature baby vulnerable to heart and brain dam-

age from lack of oxygen. This disease kills an estimated 25,000 premature infants each year.

For many years, premature infants were believed to be free of the symptoms of this disease until at least 12 hours after birth. Today, it is known that subtle signs of impending trouble show up in the delivery room. A unique grunting cry, for example, has been identified as being emitted by virtually all these infants soon after birth.

A low-cost enzyme medication, capable of preventing or dissolving the membranes that coat the lungs in hyaline membrane disease, has proved effective in tests with monkeys. At a General Clinical Research Center, this preventive medicine is undergoing trials in human infants. Hopefully, it may help cut the cost of treatment for each case from $2,000 to $40.

Ounce for ounce, the survival rate of growth-retarded babies is significantly higher than that of premature babies. However, growth-retarded newborns do sustain a higher incidence of birth defects than do the "preemies." Intrauterine growth retardation implies that some factor limited normal growth during a full-term pregnancy; this factor could also be responsible for an associated congenital malformation.

A number of cases of intrauterine growth retardation have, in fact, been traced to genetic defects. Sometimes, the defect is caused by a random aberration in the chromosomal makeup of the cells passed to a particular fetus and may affect no other prenatal germ cells.

To date, however, no genetic or chromosomal damage has been implicated as a cause of *premature* birth. Instead, premature delivery seems to be linked either to obstetrical complications or to such environmental factors as maternal cigarette smoking, exposure to high altitudes, toxemia and chronic vascular disease in the mother, or fetal infection from German measles, syphilis, or malaria. (These same factors have also been correlated with some cases of intrauterine growth retardation.)

One cause of low birth weight in both the premature and the growth-retarded baby appears to be poor nutritional status of the mother. This, however, seems to be more a function of the mother's long-term diet before pregnancy than of her diet during pregnancy. Improving the quality of an expectant mother's food intake can help her unborn baby, but it cannot totally undo the chronic nutritional deficiencies of a lifetime.

On the other hand, the mother who was adequately nourished during her own growing-up years has an excellent chance of delivering a normal size baby even if she has taken an inadequate diet during pregnancy. The "old wives' tale" holds true that the unborn child has a competitive advantage in taking the nutrients it needs from the mother—if the mother has an adequate reserve of supplies from which the fetus can draw.

No one knows if the low birth weight baby ultimately can reach his inherited potential height. There is no meaningful association between *normal* size at birth and size finally attained at adulthood. Scientists do know, however, that the smaller newborn of a set of identical twins has usually been on the "short end" of placental supply and, therefore, has probably suffered some degree of placental insufficiency. This smaller twin rarely reaches the same size as his sibling. Many scientists suspect, therefore, that during certain critical periods of growth—both during and after pregnancy—damage to the full potential of growth may be irreversible.

The Childhood Years

During the past few years scientists have started detailing the interplay between genetics, nutrition, emotions, illness, and time . . . exploring the way these factors act, sometimes singly, but more often in concert, to affect not only an individual's growth, but also his health, for better or for worse. New research techniques are providing insight into how healthy growth proceeds, what enhances it, and why boys and girls, from birth, display markedly different patterns.

Scientists are discovering that children throughout the world tend to show remarkably similar capacities for growth. Nursing infants in developing nations follow much the same pattern of growth as that considered normal for infants in the United States. The likelihood is that while each child proceeds to adulthood at his own pace, normal growth before puberty is dependent more on the life a child leads than upon the genes with which he is endowed.

The average, full-term male infant weighs 8 pounds and measures 20 inches. Some weight loss follows birth. Growth then becomes so rapid that he will probably weight 14 pounds and measure 25 inches by the age of 4 months.

After the 4th month, growth starts to slow down. Height now becomes more important than weight in evaluating the health of the growing child. When he celebrates his first birthday, the average boy should have grown to a height of 30 inches.

By the time he is 2, a child's growth begins to reflect some genetic influence. The average healthy boy then measures about 35 inches and will have reached approximately half his adult height. On his third birthday, he is close to 38 inches. His growth rate then starts to level off, and for the next 9 years, he will grow at the relatively constant rate of only 2½ inches a year.

In marked contrast to the dramatic and rapid changes that occur during the pre- and early postnatal periods, growth during the later childhood years is slowly progressive, and derangements may be subtle. Probably one of the simplest gages of a child's health status is whether he is adding inches and pounds according to accepted timetables of normal growth. The first indication that something is amiss with a child's health may be the fall of his growth curve below the third percentile for normal children. This youngster is probably suffering a period of depressed growth that should be investigated and its cause corrected.

Increase in height is due to progressive growth of bone. As noted earlier, development of the skeleton is quite incomplete at birth, and it continues to undergo many changes throughout childhood. Most primary centers of ossification, for example, develop after birth; some do not make their appearance until adolescence. Epiphyses normally are not completely closed until the end of adolescence.

Many investigators discuss human growth in terms of two ages: *chronological* age, timed from the date of birth, and *biological* age, a measure of the degree of physical maturity of the individual, determined by equating his degree of maturity with the average age at which that degree of maturity normally becomes manifest. X-rays of the bones are most often used to determine the biological age of children. The greater the number of centers of ossification present on X-ray, and the

greater the degree of epiphyseal closure, the greater is the biological age of the child—regardless of his actual chronological age. Biological age, as measured by reference to X-ray of bones, is often referred to as *bone* age.

Bone X-rays have helped establish, for example, that skeletal maturation in a girl on the day of birth is one month ahead of that of her twin brother. The female, therefore, comes into life a biologically older, more highly developed organism. It will take the male close to 20 years to catch up.

Measures of height, weight, and bone age have served as the traditional bases of growth studies. Scientists now, however, are seeking increasingly specialized techniques by which human growth may be analyzed. Enlargement of the human organism is basically the result of a myriad of chemical reactions, some of which can be measured in a short period of time by new biochemical techniques. Researchers at General Clinical Research Centers and other facilities, therefore, are now investigating individual components of growth at the tissue, cellular, and even molecular levels.

At some General Clinical Research Centers, everything the research subjects eat, drink, or eliminate is carefully measured for weight, chemical composition, and caloric value. In fact, the child who enters the bathroom without telling the nurse is interrupted by an alarm system; this prevents the loss of waste materials which must be carefully analyzed as part of precise metabolic studies.

For almost three-quarters of a century, scientists believed that growth after birth was due solely to an increase in the *size* of body cells. Now General Clinical Research Center investigators, in a new application of older knowledge, have shown that specialized cells also increase in *number* for many years after birth. For example, scientists have known for two decades that DNA is present in precisely equal quantities in the nuclei of all body cells and that the amount in each cell is constant throughout life. Therefore, from the total amount of DNA contained in a weighed muscle biopsy specimen, the number of cells constituting the specimen can be determined. Since the total weight of the specimen is known, the weight and size of each constituent cell is easily calculated. Serial repeats of such biopsies over a number of years, coupled with repeated measurement of total body muscle mass, allow investigators to calculate whether changes in muscle cell number or size have occurred.

An early conclusion drawn from such cellular analyses is that while bone maturation is an index of biological age, the number of muscle cells in the body correlates more closely with chronological age—and is related to the sex of the child. Boys and girls are probably born with the same number and size of muscle cells. By 3 weeks of age, however, the male child already has more, and larger, muscle cells than the female.

When she is 10, the girl will have undergone a fivefold increase in the number of her muscle cells; from this age, little further increase occurs in either her muscle cell size or number. In contrast, a boy's muscle cells continue to multiply until, at 18 years of age, he has 14 times as many muscle cells as he did at birth. (A tall 18-year-old boy may have 20 times more muscle cells.)

While muscle cell replication ceases at this age, some evidence exists that the muscle cells of the boy will continue to enlarge in size for another 5 years.

Once muscle cells stop growing, gross enlargement of muscle is due to an increase in the diameter of the fibrils contained inside the muscle cells. This is often brought about by conscious exercise, such as that designed to enlarge the biceps, or by the unconscious but physiological effort of a muscle to sustain a greater body function. This latter phenomenon can occur in the heart of an athlete; the fibrils of his heart may grow in size to help handle an increased workload.

Scientists have also discovered that, right from the beginning, a girl will have a greater percentage of fatty tissue, increasing in greater proportional amounts as she grows, than the boy of equal age and size. Because she has these fatty tissue reserves, a girl's external requirements for maintaining her weight are less than her brother's, and her caloric needs throughout life will be, pound for pound, less than his.

In almost every respect, the physical development of the female is more stable than that of the male. Not only is she biologically more mature, as measured by bone X-rays, but when sister and brother are exposed to the same growth-retarding condition, the girl tends to show less damage. The growth-retarded boy, on the other hand, reacts more favorably to an improvement in the condition causing his growth lag, possibly because he has more catch-up growth to accomplish.

Each successive generation in most of the industrialized world has been growing taller than the generation preceding it. On an average, young adults of today measure 1 inch more than parents and 2 inches more than their grandparents. Males, moreover, are increasing in adult height more rapidly than females. Many researchers believe these height gains can be attributed to better medical care and nutrition . . . and that the more rapid rate of increase in the male indicates how quickly his growth can respond to better times.

Will people keep growing taller and taller? No one knows. But scientists do suspect that the increase is leveling off and that, once they complete growth, today's healthy and well-nourished boys and girls will have reached the maximum height allowed by the human genetic potential.

Effects of Nutrition

A concern of scientists for over a century has been the identification of foods essential to growth. Today, they are working to define those foods that best prevent or cure childhood growth disorders stemming from malnutrition. Nutritionists are also looking into the possibility that the growth differences between boys and girls may require that the two sexes be put on different diets right from birth. And in the future lies yet another horizon: definition of the foods that result in optimal—and not necessarily maximal—body development throughout life.

As the relationship between nutrition and growth becomes understood in a more sophisticated way, the failure of a child to adhere to universal patterns of growth is not so readily ascribed, as in the past, to genetic predisposition. Instead, such deviations are being interpreted as possible signs of undernutrition or overnutrition that can be prevented and possibly cured.

Scientists know that at least 45 nutrients are basic to the maintenance of healthy growth. Lack of these nutrients over a period of time may depress appetite, encourage disease, and thus retard childhood growth. Conversely, the child whose growth rate is too slow from nonnutritional causes may also have a small appetite and decreased resistance to disease. Despite this cycle of contributing factors, precise methods of cell counting and analyzing body composition have led researchers to conclude that only two elements of diet—protein and caloric content—are of preeminent importance to normal growth.

Milk produced by an adequately nourished mother—or that provided in a specially prescribed milk formula—contains, in appropriate quantities, all protein and calories required for an infant to grow normally. Even the milk of the poorly nourished nursing mother, often deficient in volume and vitamin supply, can provide an infant with the basic nutrients required in his very early growth period.

As the child decreases his milk intake and turns to solid foods, a daily diet containing a sufficient and varied quantity of foods from the four basic groups, 1) meat, poultry, fish, and eggs; 2) vegetables and fruit; 3) milk and milk products; and 4) enriched breads and cereal, provides proper proteins and sufficient calories to allow continuing growth. Such a balanced diet will also help build up the large store of nutrients essential for the accelerated growth demands that will be precipitated later by puberty and, in the female by childbearing. For the pregnant teenager, a wholesome nutritional background is of special importance; the expectant mother who is young and still growing must meet her own dietary growth needs at the same time she is providing essential nutrients to her growing fetus.

Calories have been implicated in cell multiplication. Protein, on the other hand, may be related primarily to the ability of cells to enlarge. Scientists are beginning to suspect that failure of cells to receive sufficient proteins and calories during certain periods of body growth may lead to slowing down and, ultimately, to cessation of the ability of the cells to enlarge, divide, and develop specialized functions.

The child deprived of too many calories may never attain a normal complement of cells. Lack of sufficient protein may inhibit the size of his cells. Indeed, in some areas of the world where protein deficiency is widespread, many children have remarkably small cells for their ages.

On the other hand, the increase in the size of children, generation after generation, in the more developed nations of the world, may well be due to improved nutrition. Japanese children born after World War II are consuming a diet richer in protein by 20 percent. When they reach school, these children can no longer fit into the school desks used by their parents.

Proteins are large molecules in which various amino acids, the basic building blocks of life, are linked together in long, precise sequences. An adult needs to eat proteins that contain only eight amino acids, called the essential amino acids. A child needs a diet with a ninth amino acid, histidine.

Utilizing the amino acids in the proteins they eat, both normal adults and children go on to manufacture additional amino acids. The resulting 23 amino acids—made up from both ingested and manufactured precursors—are then regrouped chemically in the body, through a process known as protein synthesis, into the various proteins needed for specialized functions in the body. DNA in the cell nucleus dictates which of the many possible specific chains of amino acids will be manufactured by a given cell.

A new study has disclosed that a premature baby may lack the ability to manufacture cystine, an amino acid not required in the diet of full-term babies. One treatment method now being considered is to give human milk to the bottle-fed premature baby; unlike cow's milk, human milk has a high cystine content. Another possibility is to add cystine to infant formulas. These feeding methods may prove to be the desired dietary regimen for the non-nursing premature baby until he develops the natural ability to convert some of the amino acids he eats into cystine.

The deficiency of manufactured cystine in many premature infants may explain why they are more prone later to develop short height and mental deficiency than are full-term infants. Indeed, in one inherited illness, a child is never able to develop the capacity to derive cystine from other amino acids. This ailment, homocystinuria, usually results in a similar pattern of disordered growth accompanied by mental retardation.

The most common nutritional deficiency in the world caused by a chronic lack of protein in the diet is kwashiorkor. Originally identified in Ghana in 1960, kwashiorkor is now known to be rampant in most developing nations. Children with this disease suffer severe growth retardation, vulnerability to illness, swelling of the abdomen with water, and marked apathy. Kwashiorkor patients lose so much responsiveness to events around them that the treated youngster who eventually smiles is considered to be on the road to recovery.

Growth is work, and calories are the units of energy that fuel it. Carbohydrates and fat calories are the most readily available to supply the body's energy needs, but protein as well can be burned for energy. If excess calories are eaten, a few of the unused ones are converted to glycogen, and the remainder are stored as fat.

If insufficient calories are eaten, the body will first use up its caloric stores to meet its energy needs. Then it will begin to devour itself by consuming structural protein. During the years of childhood growth, extreme deprivation of calories results in marasmus, a condition marked by extreme wasting, emaciation, and starvation of body tissues.

In developing nations, an estimated 300 million children suffer from marasmus, kwashiorkor, or a combination of both. Both diseases are usually precipitated by the weaning process and the withdrawal from the infant of his near adequate nutrition. After the mother ceases to nurse her infant, the baby's life is marked by recurrent diarrheal infections from unhygienically prepared foods. He is also affected by the inability of his poverty-stricken mother to find fruits, vegetables, grain, and edible underground shoots that might make up an adequate diet. This interaction between infectious disease and malnutrition is the primary reason why deaths in the 1-to-4-year-old group are 50 to 60 times greater in developing regions of the world than in the United States.

Fortunately, new biochemical methods for determining the nature and extent of protein and calorie deficiencies are leading to new kinds of nutrition therapies. Some cases of kwashiorkor, for example, may now be prevented by the use of newly developed protein foods made from cottonseed flour or other vegetable sources; they are usually less expensive and more readily available than animal protein.

The greater his degree of malnutrition, the higher the caloric intake a child needs in order to grow at a satisfactory pace. This appears to hold true regardless of whether the malnutrition was due primarily to deficiency of calories or of protein.

The traditional therapy of children who have already undergone the rigors of severe protein and calorie malnutrition has been a high-protein diet. Studies show, however, that after the first few days on such diets, malnourished children react as do other growing children who receive insufficient calories. Their bodies use the protein for energy rather than for growth, and growth remains retarded.

Recently, a number of marasmic and kwashiorkor children have shown significant benefit from a new kind of diet which is only minimally adequate in protein but very high in calories. Children treated on the new diet usually achieve the proper weight for their height in 8 weeks and are then strong enough to leave the hospital. As the diet is maintained at home, the treated child continues to grow taller until his height is equal to that of his "normal" siblings. However, they are probably shorter than they should be as a result of their own share of inadequate diets.

Youngsters treated with the minimal protein, high-calorie diet have also been shown to have better long-term resistance to disease and to have less recurrence of severe malnutrition at home. They were contrasted to malnourished children whose long-term hospital therapy stressed high protein intake.

Until recently, severe malnutrition among children was thought to exist only outside the borders of the United States. No truly reliable count exists of the number of people in this nation who suffer primary malnutrition, due to inadequate diet. However, the first comprehensive survey of the nutritional status of the lowest economic quarter of the U.S. population is currently being conducted by the nutrition program of the Department of Health, Education, and Welfare. Surprisingly, the program is documenting that protein and calorie deficiency does exist in this country, sometimes in marked degree. This is particularly true among children in poverty areas on Indian reservations, in Appalachia, in the Southeast, and in large city ghettos. Studies show that the average height of poorly nourished American children in the 1-to-6 age group is from 5 to 15 percent lower than that of their well nourished contemporaries.

An alarming finding is that many children in the United States even suffer kwashiorkor or marasmus. Because low-income American mothers seldom breast feed, their children are often denied the initial period of near normal growth enjoyed by children nursed by mothers in even the poorest of countries. Marasmus or kwashiorkor, superimposed upon this early deficiency, may prove to be even more detrimental to affected children in the United States than to those in nations where the diseases are endemic.

Few American youngsters starve to death. Yet, there is justifiable concern over the long-term hazards of their nutritional deficiencies. A few years ago, many studies suggested that even after the causal nutritional deficiencies were corrected, children with below-normal head size, height, and intelligence, incurred between the ages of 2 and 7, might never sufficiently catch up. Some scientists estimated that the brain cell count in nutritionally deprived children might be 20 percent below normal when adulthood was reached. (A number of other studies indicated irreparable damage in the brains of young farm animals deprived of protein.)

New head size studies of older children whose dietary deficits were corrected, however, show that some of the original head measures were in error. Latest figures reveal that head size (and presumably brain size) frequently does increase in proportion to the catchup height being attained by treated children. A number of growth experts, therefore, today believe that the neurological impairments seen in some undernourished children are caused not by faulty diet but rather by the debilitating emotional conditions under which many of these children are raised.

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Current scientific opinion is that nutritional deprivation incurred before 4 months of life can often be speedily and permanently remedied by a proper diet. After the child is 4 months of age, the more severe the malnutrition and the earlier it occurs, the more marked, and perhaps permanent, appear to be the adverse effects produced on any system in the body (including the nervous system). Indeed, in one study of the effects of diet on the intelligence of American youngsters, the only subjects who showed normal IQ's at age 3½ were those whose malnutrition was arrested before they were 4 months old.

However, much more work remains to be done to determine precisely how mental deficiencies, as well as impaired height and weight, are incurred in malnourished children, and whether and when the defects become permanent.

In contrast to studies hinting at possible irreparable damage inflicted by under-feeding of children, new cell-counting techniques paradoxically also indicate that about 8 percent of youngsters in affluent nations are being overfed.

Obesity in many children has origin in infancy. Since infants tend to regulate their food intake by volume rather than by nutritional content, they often consume inordinate quantities of formulas highly concentrated in calories and protein. One theory is that this unconscious gluttony may stimulate into existence excessive numbers of fat storage cells and, thereby, trigger in many infants a genetic predisposition to overweight that can plague them throughout adult life.

Once a fat cell is stimulated into existence by excess caloric intake in infancy, it is possible that neither time nor diet can make that cell disappear. Some scientists believe that a fat cell can shrink only in size, leaving that cell lurking in wait for the extra fat that can fill it again. Other researchers believe that just as fat cells can "come," so it is possible that weight loss can make them "go."

Scientists at a General Clinical Research Center have already identified one group of overweight boys who weigh at least half again the optimum for their age. In them, gross overweight is correlated with infant overnutrition, advanced bone age, larger skeletal size, minimal physical activity, and three times the normal number of fat cells.

General Clinical Research Center studies have also shown that obese adults of both sexes have excess fat cells. However, they have also shown that whereas young obese boys have too many fat cells, young girls do not. As there is a possible correlation between coronary artery disease and long-term burdens imposed on hearts pumping blood through excess fatty tissue, such basic studies as these, in children, may eventually provide researchers the essential clues to discover why heart ailments are more common in men than in women.

Today, the important relationship between nutrition and growth has begun to assume its rightful place in the diagnosis of growth problems. Scientists conducting indepth investigations of rates that are either too slow or fast now consider under- or over-nutrition as one of the major probable causes of deviation from the normal.

Effects of Hormones

Interaction of the hormones produced by the various endocrine glands in the body constitutes an important chemical control system for major body activities. Derangement in secretion or activity of a single hormone can produce serious disruption of this interlocking system and adversely affect growth in many ways. New measurement techniques are today allowing investigators to study the actions and interactions of hormones with greater precision than ever before and, from such research, to develop more effective methods of treatment for patients with severe hormonal disorders.

The biochemical analysis of hormones was revolutionized in the 1960's by the development of radioimmunoassay—a laboratory test that can measure in body fluids one thousandth the amount of a hormone previously detectable. This complex technique makes use of the precise specificity of antibodies developed to the hormones being measured and of the ability to attach radioactive labels to these antibodies such that they may be followed accurately through a series of chemical reactions. The potential of this technique in the study of basic hormone chemistry cannot be overestimated. A measure of its considered importance within the scientific community is the fact that radioimmunoassays have been or are in the process of being developed for practically every known hormone in man.

Although synchronized activity of all hormones in the body is necessary for appropriate patterns of growth, human growth hormone (HGH) and insulin are the two presently considered as fundamental to normal growth processes.

Growth hormone is secreted by the pituitary gland—a pea-sized organ attached by a stalk of nervous tissue to the base of the brain. HGH has been identified in fetal blood as early as 15 weeks after conception. So far as is known, it continues to be produced by the pituitary throughout life. Radioimmunoassay has demonstrated that, in the normal individual, HGH is released in bursts of intermittent activity. Scientists at one General Clinical Research Center have shown, for the first time, that peak HGH release occurs between 60 and 90 minutes after the onset of nocturnal sleep.

The growth-promoting activity of HGH was the first characterized, and from this activity, the hormone was named. However, evidence is accumulating that HGH in fact serves as an overall regulator of many metabolic processes in the body and that its influence on growth is only the result of these separate activities. For example, radioimmunoassay studies have confirmed that the release of HGH into the blood stream is promptly and massively stimulated by a fall of blood sugar levels. This and other studies indicate, therefore, that growth hormone may be fundamental to the use of caloric energy in the body and, thereby, may exert control over the way cells multiply in number. (Since HGH may be implicated in the multiplication of cells, research on its biochemical activity may in time open an approach toward the study, and possible cure, of cancer.)

Insulin traditionally has been assigned the restricted role of promoting the transfer of sugar from the blood stream into the cells, where its

energy can be utilized to drive body activities. Diabetes, in which insulin is deficient, is characterized by the unavailability to cells of the energy of sugar, despite its presence in the blood stream in pathologically elevated amounts. However, insulin too is beginning to be assigned a larger role in the human growth process.

Before insulin injections were available as treatment, many juvenile diabetics who survived to adulthood were of remarkably short stature and were known as "diabetic dwarfs." Therefore, in addition to its effect on sugar metabolism, insulin may have a profound effect on protein synthesis, the process involving manufacture and buildup of protein molecules within the body. This effect, in turn, could have great significance in the regulation of the size of cells in the growing human and, ultimately, of the overall size of the adult body.

In addition to increasing our fundamental knowledge of the growth process, study of insulin's effect on growth may also provide an understanding of why the pancreatic cells of some growth-retarded children fail to secrete insulin effectively, and why severely malnourished children often have remarkably small cells for their age.

Gross defects in human growth hormone secretion have long been recognized clinically by the disordered growth patterns they produce. Congenital undersecretion of HGH gives rise to hypopituitary dwarfism. The most important developmental characteristic of the hypopituitary dwarf is that while he usually is normal size at birth, and may grow normally for the first 2 or 3 years of life, he rarely grows more than 1½ inches a year after the age of three. His growth, however, is proportionate, and there are no deforming or unusual features. Intelligence is unaffected, and appetite is normal for size.

Because of the interaction between HGH, insulin, and blood sugar levels, the hypopituitary dwarf can be exquisitely vulnerable to insulin. Since its effect is not opposed by the contrary action of HGH, a very minimal injection of insulin in these patients can produce a profound fall in blood sugar.

Radioimmunoassay tests have indicated that deficient production of growth hormone in hypopituitary dwarfs may actually begin in the first few months of life. In some instances, the insufficiency stems from a tumor in, or an injury to, the pituitary gland. In most cases, however, the reason for the low HGH production by the pituitary is completely unknown. Also unknown is why hypopituitary dwarfism is twice as common among boys as among girls and why it is frequently accompanied by delayed sexual maturation.

In the late 1950's, scientists discovered that injections of growth hormone extracted from monkey pituitary glands increased the rate of growth of hypopituitary dwarfs. The amount of the hormone obtainable from monkey pituitaries was, however, so minute that a method was developed to secure the larger amounts available in the pituitary glands of human cadavers.

The best test of the effectiveness of HGH injections is the fact that growth during therapy increases to two to three times the rate before treatment. Typically, the child grows 2 to 3 inches in the first few months of therapy. Within the first year, a total growth of 3 to 5 inches generally takes place.

Since 1958, human growth hormone has been used in the treatment of an estimated 2,000 hypopituitary dwarfs, most of them as part of research protocols in General Clinical Research Centers. Thus far, the most common adverse reaction reported has been "the pain of the shot."

The degree and duration of responsiveness to HGH administration, however, are variable. Blood tests reveal that three-fourths of all treated patients develop antibodies to administered HGH. This antibody formation markedly reduces the growth stimulation of the injected hormone. In some instances of extreme antibody reaction, patients develop a treatment insensitivity which causes them to stop growing entirely. Unfortunately, in one out of every 10 to 20 patients, resistance to the injected hormone results in a complete halt to growth long before the desired increase has been attained.

Each week of treatment for the average hypopituitary child requires the hormone extracted from two human pituitary glands. At present, only one-tenth of the human growth hormone needed for both research and treatment is available in this country. Since only 10–15 percent of all dwarfism is caused by a lack of HGH, the small hypopituitary group is the only logical one for hormone replacement therapy. The radioimmunoassay test has replaced the crude measures previously used to determine HGH blood level. In addition to enabling positive identification of the disorder so that precious supplies of HGH might be conserved, the sensitivity of this test also allows clinicians to make the diagnosis of hypopituitary dwarfism, and initiate treatment, long before retarded growth has progressed to the point that the condition is clearly apparent but irreversible.

HGH supplies remain in such scarcity that priority for treatment is highest in the older child whose epiphyses are near closure; once epiphyses are closed, growth cannot be resumed by any known means. Also, in order that the limited supply of HGH may be allocated to the maximum number of patients, therapy must usually be discontinued once a child is brought up to the height of 5 feet.

In 1963, as part of an effort to secure larger quantities of HGH for research and treatment, the College of American Pathologists and the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health established the National Pituitary Agency. Pituitary glands can be willed to this organization. In addition, the Agency is part of a cooperative project, in which many General Clinical Research Centers are included, that is attempting to define the most economical and effective dosage schedule of HGH. Finally, a search has been launched for another growth hormone preparation which either can resist antibody formation or which, for whatever reason, does not have a waning effect on growth.

One of the studies showing promise at a General Clinical Research Center is the use of human placental lactogen as an HGH substitute. This hormone, manufactured normally by the placenta during pregnancy, may have a growth hormone effect on the growing fetus and, therefore, may be a useful preparation to administer to children of short statu . At present, however, the process of refining human placental lactogen remains too expensive and time consuming to allow its use as a practical alternative to HGH for therapy.

Another line of research derives from the fact that growth hormone removed from human cadavers is an extremely large protein molecule. That portion wherein the growth-stimulating activity is located—the active site—likely constitutes only a small portion of the entire molecule. If this active site can be identified and its structure analyzed, its relatively small size should make possible the manufacture in the laboratory of a synthetic growth stimulator in quantities sufficient to treat all deficient children.

In fact, an initial effort to isolate this site chemically has recently proved successful. The synthesized protein contains 188 amino acids. Although it is only a small portion of the complete HGH molecule, its synthesis is one of the most complex achievements to date in protein chemistry. The protein at present is only 10 percent as active as human growth hormone; therefore, the process of analysis and synthesis must be further refined before a compound sufficiently potent for patient therapy can be made. However, when that day comes, pediatricians may be dispensing a growth hormone to hypopituitary dwarfs as readily as they now provide insulin to young diabetics.

Deficiency in HGH during the period of childhood growth is but one of the defects which may be associated with the hormone. Giantism and acromegaly, both extremely rare disorders, result from excess secretion by the pituitary of 2 to 10 times the normal amounts of growth hormone.

If excess secretion of HGH occurs during childhood or puberty, when the epiphyses are open and bone growth can still occur, its overabundance causes the long bones to undergo enormous size increases, and giantism results. Acromegaly, on the other hand, occurs when excessive HGH secretion begins only after the epiphyses are closed. In this disorder, since no further growth in the length of long bones can occur, the overgrowth produced is disproportionate; a patient's height may remain the same, but there can be grotesque increase in size of fingers, toes, forehead, jaw, and internal organs.

Usually, both patients with acromegaly and patients with giantism have markedly elevated secretions of insulin. As insulin tends to decrease blood sugar levels and human growth hormone tends to elevate them, this hypersecretion of insulin is probably a physiologic compensation by the body to maintain blood sugar at normal levels in face of the tendency of the excess HGH to elevate them. Frequently, over time, the ability of the pancreas to secrete insulin is exhausted, and the patient develops clinical diabetes.

As in so many areas of endocrinological research and treatment, the radioimmunoassay method to measure hormone levels has dramatically improved the outlook for potential giants and acromegalics. The effective treatment for either condition is the removal of the pituitary surgically or its destruction by radiation; however, all excess growth which has occurred prior to the time of pituitary ablation is permanent and cannot be reversed. Since radioimmunoassay allows physicians to detect pathologic hypersecretion of growth hormone very early, both diseases may now be diagnosed and treatment instituted long before body growth has become obviously, and irreversibly, distorted.

In addition to growth hormone, the pituitary gland secretes other hormones which are indirectly related to growth. These trophic, or sustaining, hormones control the secretion of other hormones more directly involved in human growth. The trophic hormones are thyrotrophin (which stimulates the thyroid gland to secrete thyroxine), the adrenocorticotrophic hormone, ACTH (which stimulates secretion of steroid hormones by the cortex of the adrenal glands), and the gonadotrophins (which control production of sex hormones from the ovaries and testes).

There is a feedback mechanism by which each of the hormones stimulated in turn regulates the release of its own trophic hormone. The stimulated hormones first act on the hypothalamus, the area at the base of the brain to which the pituitary stalk is attached. The hypothalamus in turn releases chemical substances which flow through specialized veins to the pituitary gland and which inhibit or stimulate the release by it of trophic hormones.

Thyroxine, produced by the thyroid gland (a mass of endocrine tissue located in front of the windpipe), was one of the first hormones to be identified as important in growth regulation. Thyroxine alone is not capable of producing normal growth; however, its presence is essential for normal growth to occur. Some hypopituitary dwarfs lack sufficient quantities of both thyroxine and human growth hormone. They will grow only if thyroxine is administered concomitant with HGH.

As opposed to growth hormone deficiency, which produces proportionate short stature and no loss of intellect, thyroxine lack during the growth years can result in stunted growth in which bone development is disproportionate and mental capacity almost invariably defective.

The disorder can start during the prenatal period. If fetal thyroid tissue develops inadequately during pregnancy, the affected newborn may be severely retarded both intellectually and physically. Although such congenitally deficient children, known as cretins, have a good chance of attaining normal stature if thyroid therapy is instituted at the time of birth, only a small number are ever able to attain normal mental capacity.

Today, a pregnant woman who is expected to give birth to a cretinous child is given massive doses of one of the thyroid hormones. Because of concentration effect, some of the hormone passes through the placenta and permits the fetus to develop normally. After birth, for normal growth to occur, the child must continue to receive the hormone throughout life.

A deficiency of thyroxine, which begins at any time after birth, is known as hypothyroidism. For unknown reasons, a growing child with hypothyroidism has excessively large cells and, therefore, a reduced number of cells for his body size. He grows at one-half the normal rate, and if the condition remains untreated, he can develop all the symptoms of cretinism. In an affected child, thyroxine treatment restores cell size to normal and increases growth to three times the pretreatment rate until his size again approximates that normal for this age.

Cortisone, a steroid hormone put out by the cortex of the adrenal glands, is essential to a number of physiologic functions. It requires pituitary adrenocorticotrophic hormone (ACTH) for its secretion. Since hypopituitary dwarfs also tend to have low levels of ACTH, both cortisone and HGH must sometimes be administered to them. Unfortunately, the dominant effects on growth of cortisone oppose those of HGH. For example, children who secrete normal amounts of HGH but for various reasons require cortisone therapy frequently experience slowdowns in growth. Consequently, investigators at a number of General Clinical Research Centers in recent years have traced the lack of therapeutic response to HGH seen in some hypopituitary dwarfs to the competitive activity of concurrently administered cortisone. When the cortisone regimen is eliminated or, if essential, its dosage schedule optimally adjusted, these patients immediately spurt in growth.

The male hormones (androgens), of which testosterone is the one best characterized, are excreted by the testes. The female hormones, estrogen and progesterone, are secreted by the ovaries. However, in both sexes both female hormones and androgens are also excreted in relatively small, appropriately different amounts by the cortex of the adrenal glands.

The output of *adrenal* androgens in boys and girls is radically increased during puberty, when the adrenal glands become unusually responsive to ACTH. Recent scientific information indicates that the increased androgens initiate the growth spurt preceding adulthood, help prepare the body for its adult reproductive function, and stimulate, in concert with other hormones, the closure of the epiphyses. Therefore, although androgens stimulate the adolescent growth spurt through their action on epiphyses, they also promote the process by which bone growth is terminated. The final stature attained by a young adult is in part the resultant of these two conflicting activities.

Two remaining hormones are of particular significance in the growth of human beings—calcitonin and parathormone. Calcitonin, a recently discovered hormone, is a regulator of calcium and is excreted by the thyroid gland. Current opinion holds that calcitonin production is stimulated by an *increase* in calcium levels in the blood. The hormone, in turn, promotes the uptake by bone of calcium and thereby leads to reduction of blood calcium levels to normal.

Parathormone is excreted by the parathyroids, tiny glands imbedded in the thyroid gland. Parathormone excretion is stimulated by a *fall* of blood calcium levels. Through a number of mechanisms, one of which is the promotion of calcium flow from bone into the blood stream, it acts to increase blood calcium levels to normal.

The two hormones, although derived from different glands, together function as an exquisitely sensitive control mechanism to maintain blood calcium levels within closely defined normal limits. Their principal importance to human growth seems to be their influence on the mineralization of bone. Derangement in secretion of either can have profound effects upon the development of bone and, thereby, on the entire growth process.

Of curious interest is the fact that of all the many hormones which are important in the regulation of human growth, calcitonin and parathormone are the only two, so far as is known, which are not under the direct control of the pituitary gland.

Effects of Illness

Steady continuous growth during childhood requires careful synchrony of body activities and efficient utilization of energy available. Any illness which disrupts this synchrony or which diverts excessive energy to itself will likely disrupt or retard normal growth processes. Study of the relationship between illness and growth is of particular importance in that many growth disturbances evolve so slowly they are unapparent clinically, or even on X-ray, until the stage at which irreversible damage has occurred. Conversely, an observable growth deformity may be the first, and sometimes the only, sign of a number of underlying causes which, if not detected and overcome, may have adverse effects far more serious than the growth disruptions they produce.

The entire physiology of the child is built around the growth process. Unless a health problem intervenes to block his inherent tendency to grow, a youngster rarely stops working to achieve appropriate increases in height and weight; however, investigators remain mystified as to how many diseases produce their detrimental effect.

Some disorders slow proportionately the entire growth process. Congenital deficiency of human growth hormone produces a form of dwarfism in which a normally proportioned small adult results. Other disorders affect only one component of growth, making it disharmonious. For example, desultory inflammation of epiphyses can prematurely fuse the growing ends of bones and shorten permanently one or more affected limbs.

Many illnesses produce adverse effects on growth by compromising the ability of the body to function at peak health. A common example is secondary malnutrition, in which an intestinal obstruction or cellular anomaly interferes with the proper absorption and use of food.

Fifteen years ago, there were few remedies for secondary malnutrition. Medical research has since progressed to the point that restoration of adequate nutrition in affected children is now the rule rather than the exception.

One specific form of secondary malnutrition for which therapy is available is found in those infants who lack a digestive enzyme needed to convert the sugar in cow's milk to a kind that can be absorbed. This condition exists in 70 percent of American Negroes. In adults, of course, the enzyme deficiency is annoying but not life- or growth-threatening. However, since cow's milk is virtually the entire diet of most newborns in the United States, infants lacking the enzyme frequently suffer severe diarrhea, intense discomfort, and pronounced growth retardation. In more severe cases, the infant may die. Scientific investigators have developed soybean and other non-milk formulas which contain sugars that can be digested and absorbed by affected newborns. These formulas can totally alleviate the ill effects of the enzyme deficiency.

Another secondary form of malnutrition which can retard growth is sprue. At one General Clinical Research Center, studies have shown that in sprue patients, gluten—a protein found in many cereal flours—stimulates abnormal structural and functional changes in the cells lining the intestinal wall. These abnormal changes inhibit the young child's ability to absorb nutrients into the blood stream. Most ill children who are placed on a gluten-free diet recover their health and within a year begin to grow normally. Many subsequently lose entirely their abnormal sensitivity to the wheat protein and are able to return for the remainder of their lives to normal diets.

In general, therapeutic diets have been, or are in the process of being, developed for a wide variety of food-related disorders that can produce growth retardation. As in the case of sprue, some diets have been developed in which a single damaging nutrient is omitted. In other diets, a precursor of an unabsorbable substance, such as a vitamin, is fed in such large quantities that some of it is by concentration gradient forced through the intestinal wall into the blood stream and subsequently converted into the needed dietary product.

Infants with chronic diarrhea, congenital physical obstruction of the esophagus, ineffective swallowing reflexes due to prematurity, or a host of other difficulties that prevent the proper intake and intestinal absorption of food can now frequently be nourished through use of a new technique developed at a General Clinical Research Center. The new technique—intravenous hyperalimentation—allows the stomach and the intestines to be bypassed completely; amino acids, fats, sugar, vitamins, and minerals are all injected through the veins directly into the blood stream, from where they may be taken up directly by the cells.

Vitamins are chemical compounds, normal constituents of a balanced diet, which are necessary for a number of metabolic processes in the body. Childhood deficiency of any of the many known vitamins can lead to serious distortions in growth. Too, particularly in highly developed nations, scientists have in recent years been characterizing disorders resulting from excess intake of a number of vitamins.

Vitamin A deficiency, for example, has long been known to thicken the long bones of a growing child and lead to growth retardation. A more recent finding in the United States, however, is that excess intake of vitamin A may also produce growth failure. Bone modeling is speeded up, and thin bones are developed which are prone to fracture and sometimes fatal internal hemorrhage. Many clinical investigators now believe that the use of vitamin A supplements in foods represents an unnecessary hazard to the growing child, particularly since most children in this country derive sufficient amounts of vitamin A from their diet.

Vitamin D is required for the uptake of calcium from the intestine and is thereby essential for the adequate mineralization of growing bone. Its absence in the diet can give rise to rickets—a disease characterized by soft bones, bowed legs, and cartilage that fails to mineralize adequately. In the late 1930's, irradiated milk was put on the market, making vitamin D readily available in the diets of most infants and children, and rickets began to become in this country a disease of the past.

Recent research findings have indicated, however, that a small number of children have a lowered response to vitamin D and may appear deficient despite an adequate amount of the vitamin in the diet. The insensitivity, which does not become of importance until after birth, is caused by a number of different biochemical abnormalities, may show several distinct patterns of inheritance, and can present an unpredictable variety of symptoms. Some of the victims are short but not dwarfed. Others may develop signs and symptoms of classical rickets within months or even years after birth.

The most common form of the disorder is a condition known as primary hypophosphatemic vitamin D resistant rickets. The condition is frequently sex-linked; a mother carrying the abnormal gene may be without the disease herself and yet pass the gene and the resulting clinical disorder to a son. The inability to respond adequately to normal amounts of vitamin D may also be due to a second disorder in which the kidneys fail for some reason to reabsorb sufficient quantities of phosphorous. The unabsorbed mineral escapes in the urine and is unavailable for incorporation into growing bones.

Until recently, therapy for both of these disorders consisted of administering massive amounts of vitamin D in order to build very high blood levels. This therapy was thought to work due to the "pressure" of the high concentration of the vitamin overwhelming a block in a defective biochemical pathway. Such therapy, however, had to be exceptionally judicious because very high levels of vitamin D can produce serious injury to the kidneys.

Partial circumvention of this possible side effect resulted from a therapeutic innovation of one General Clinical Research Center. There, investigators initiated use of a secondary form of vitamin D which works more quickly, is used up more rapidly, and therefore incorporates less threat of injuring the kidneys than does an overload of the primary natural form.

An even more promising therapy has recently been reported by researchers at another General Clinical Research Center. Scientists there theorized that a patient's inability to utilize normal amounts of vitamin D might be due to deficiency of an enzyme which in normal people acts to convert the natural vitamin into an active form. To evaluate this premise, they administered increasingly large, thrice-daily doses of the *activated* vitamin D to five patients insenstitive to the natural form. During 10 months of treatment at the research center, dramatic clinical, chemical, and X-ray improvements have been observed, and there is to date no evidence of side effects or kidney damage.

Recent evidence has indicated that parents who carry genes for a vitamin D insensitivity, and who do not display the full form of the disease themselves, have, nevertheless, certain blood abnormalities which reflect the genetic defect. A low concentration of phosphorous in the blood is one of the abnormalities. If vitamin D insensitivity has shown up in his family tree, and if one parent has low blood phosphorous, an infant should be tested early to determine if he has inherited, and will eventually exhibit, vitamin D insensitivity .

Early diagnosis is of great significance because therapy before 6 months of age usually averts completely the bone deformities and the growth retardation that might otherwise result. Treatment begun at a later age can heal the lesions and possibly speed up growth, but no one knows if delayed therapy can in time fully restore a child to his optimal pattern of growth.

A third inherited lack of vitamin D responsiveness, which also may cause growth retardation and rickets, is renal tubular acidosis. This condition is caused by excessive excretion in the urine of bicarbonate, which is alkaline. The result is an excess retention of acid within the body. This body state, known as acidosis, in turn causes excess elimination of phosphorous in the urine. Consequently, insufficient phosphorous circulates in the body fluids, and bone mineralization is defective.

Fortunately, total control of renal tubular acidosis is now achieved through the simple technique of feeding sodium and potassium citrate in palatable fruit-flavored bases. The citrate is metabolized into bicarbonate, replacing that lost in the urine. A normal acid-alkaline ratio is maintained, and proper mineralization of the bones can then occur.

In recent years, concern has been expressed that many children are ingesting too much, rather than too little, vitamin D, and that this excess may cause growth retardation. Recent studies have shown that many children do indeed receive moderate overdoses of vitamin D and that, consequently, they may absorb more calcium into the blood stream than they need. This excess calcium has not, however, been related to any growth impairment in normal children.

Occasionally, a child does turn up at a General Clinical Research Center suffering from severe hypercalcemia—a blood level of calcium sufficiently high to produce deflection in the course of growth. A prevailing theory holds that such children have inherited a grossly exaggerated response to even normal doses of vitamin D. When placed on low calcium diets, these children show remarkable growth improvement.

As scientists isolate more and more disorders which affect human growth, an increasing number, such as vitamin D insensitivity, are proving to be errors of metabolism genetically decreed at the moment of conception.

The structure of proteins synthesized within the body is determined by the DNA within the nucleus of cells. Derangement in the placement or internal makeup of a single gene within the DNA can so distort protein synthesis that a protein of markedly abnormal structure is produced. If this protein is integral to an important biochemical pathway, the pathway may be blocked. Chemical substances normally degraded or otherwise acted upon by the pathway may build up to pathologically high levels, and essential products of the reaction may be produced in seriously deficient amounts. The effect on the growth process of this inherited block depends upon the importance of the pathway, the availability of alternate competent pathways, the age at which the blocked pathway becomes significant, and, finally, upon the external factors operating concomitantly.

Sickle cell anemia is an inherited cause of growth retardation which is found only among black people. This trait may have evolved as a valuable adaptation to life in Africa, where malaria is endemic. The abnormal hemoglobin responsible for the unique sickle shape of the red blood cells provides resistance to malaria parasites. Chronic anemia, however, results because of a decreased capacity of these sickle-shaped blood cells to carry oxygen.

Children with this inherited disorder may grow within normal limits; however, one study has shown that, as a group, they weigh less, are shorter, and have a thinner body build than either their normal siblings or normal nonblack children. Repeated blood transfusions, given in the past to affected children as a research treatment, temporarily relieved them of anemia and placed them in higher growth curves. Therapy had to be discontinued, however, because the ill effects produced by repeated transfusions were found to pose a greater threat to health than did slow growth. The researchers felt that in view of the limited ability of these children to oxygenate additional tissue, being small might well be an advantage.

A much more rare, but treatable, inherited ailment is acrodermatitis enteropathica. This disease, which may be fatal if left untreated, is characterized by dwarfism and persistent fungus infections of the skin. It results from an inability of the affected child to manufacture or metabolize the unsaturated fatty acids needed to maintain growth and skin integrity. Breast feeding prevents expression of the disease for a time. Cow's milk, which has a higher proportion of nonhuman unsaturated fatty acids, exacerbates it.

A number of infants severely ill with acrodermatitis enteropathica are today responding dramatically to simple injections of cottonseed oil. Once these injections bring the disease under control, a drug which has been used for over half a century to treat yeast infections unexplainedly can take over to control all further symptoms. In fact, only now is it apparent that some adults who, as children, had been routinely prescribed the drug for yeast infections might well have "grown up" to be dwarfs had not their basic disease been accidently treated at the same time.

The need for the drug persists throughout life. Investigation has just been launched to study the drug's relation to fatty acid metabolism and to determine how it works.

Acrodermatitis enteropathica and its empirical treatment is a prime example of how science can often control a genetically determined metabolic error even before the underlying biochemical defect is fully understood.

In recent years, great strides have been made in identifying and distinguishing an array of enzymatic malfunctions, all of which result in disproportionate dwarfism. Individuals affected with these enzymatic disorders, who were once given the catch-all diagnosis of achondroplasia, tend to possess a normal length trunk; however, their limbs are too short and their heads are too large for either their chronological or biological age. The lack of synchronous growth is due to the fact that the formation of cartilage, and its replacement with bone, is irregular throughout the skeleton.

Classical achondroplasia has now been identified by a General Clinical Research Center as a *specific* illness in which cartilage formation actually proceeds in an orderly fashion; subsequent bone formation, however, is too slow to keep pace with both the normal development of connective tissues covering the bones and the closing down of the epiphyses.

The same General Clinical Research Center has shown another type of disproportionate dwarfism to result from markedly disordered cartilage formation. During the prenatal period, this disorder can result in an abnormally narrow chest which, by restricting breathing, can cause death soon after the newborn becomes dependent on his own lung capacity.

As in vitamin D insensitivity, when a growth disorder is inherited, the defective gene may have also expressed itself by an observable abnormality in the parent. More often, however, the genetic aberration in one strand of parental DNA is overcome by the normal functioning of the paired gene in the parallel strand of DNA; in this case, the resulting illness is minimally or not at all detectable in the parent. The aberrant gene is then said to be *recessive*. Its adverse influence is overcome by the normal, or *dominant*, gene with which it is paired.

If both parents contain a recessive abnormal gene controlling the same function, one out of every four children produced by the two will likely receive a pair of recessives, one from the germ cell of each parent. The affected child will have no dominant normal gene, and the abnormal function will be expressed fully in him.

The recessive method of inheritance is common to a wide variety of genetic disorders. (Other inherited metabolic errors have more complex methods of transmission.) Sometimes, however, the metabolic error may represent a fresh mutation in an isolated gene. This mutation may result from an external influence such as German

measles, parental age, radiation, or drugs acting adversely on either the germ or the fetal cells. In such cases, there is no statistical pattern of inheritance, and parents of an afflicted child need have little fear of recurrence in future offspring.

One illustration of a fresh mutation resulting in a slow rate of growth after birth is mongolism or Down's syndrome. Only one-half of 1 percent of parents stand a chance of bearing such a child; this rate applies whether or not the family has already had a mongol child. The disorder cannot be cured, but since fetal cells are constantly cast off into the amniotic fluid in which the growing child is suspended, amniocentesis by the 14th week of intrauterine life can now reveal if the fetus is carrying the defect.

Turner's syndrome and Hurler's syndrome are two other classic examples of inherited, potentially growth-retarding diseases which can be diagnosed in intrauterine life by amniocentesis.

Minor symptoms which are themselves of little immediate consequence to the patient may serve as diagnositic clues to serious illnesses which may in the future severely retard growth. For example, only recently has it been discovered that a combination of slightly elevated temperature, greater than normal intake of oxygen, numerous nosebleeds, and excessive perspiration can hint at the presence of osteogenesis imperfecta. This disorder in time results in bones which are brittle, thin, and fragile; an afflicted infant can suffer broken bones just from having his diaper changed. The bones in the ear are also frequently affected. Some cases are inherited from parents with defective genes; others are the result of fresh genetic mutations.

The affected child usually grows normally at first. But, over the years, growth becomes stunted, and repeated fractures keep him not only from normal play but even from attending school.

Until 1968, no medical help was available. Now, during a second year of experimental treatment, osteogenesis imperfecta patients who have been prescribed capsules of magnesium oxide are demonstrating a 50-percent reduction in fracture rate and are putting on needed weight. Since the bones of many treated patients have already undergone irreversible deformity, the ultimate effect of this medication on height gain is still too meager to assess. However, investigators feel that the earlier the diagnosis is made and therapy initiated, the greater is the chance that the affected child may achieve near-normal patterns of growth.

Growth of children born with heart disease, whether congenital or inherited, often lags as much as 2 years behind that of their peers. By the time the child with a severe congenital heart condition reaches his fifth birthday, he may be burdened with a 1½-year growth lag. Extensive studies of these youngsters are being conducted by investigators at a number of General Clinical Research Centers.

One finding is that the severity of the growth lag tends to parallel the severity of the heart defect. In only a limited number of specific heart disorders, however, does growth retardation seem to stem directly from a reduced ability of the heart to circulate blood to the growing body tissues.

Clinical research center researchers have also found that many children with heart disease have an almost normal number of body cells for their size but not for their age. Some of the cells are abnormally large, while others are abnormally

small. These cellular anomalies may result from an inefficient transport into the cells of amino acids needed for protein synthesis, or they may result from excessive whole body intake of oxygen. They could also result from unknown effects of heart ailments which stimulate or inhibit calorie or protein metabolism.

In almost all cases in which an underlying illness has retarded growth, the stunted child can show almost magical powers of compensatory growth once the illness has been adequately treated. Not all heart victims improve their growth rate after corrective surgery, but in most acceleration does take place within 2 years following the correction. The most dramatic growth is experienced by a child in whom a major, congenitally narrowed artery between the heart and lungs is widened surgically. This youngster can gain as much as 4 years of biological age within a 6-month growth spurt, which brings him near the same point he would have reached had he never suffered the defect.

In other examples, the growth of one 12-year-old boy successfully treated for hypothyroidism accelerated to the rate experienced by a 1½-year-old child. Once a 4-year-old girl had a tumor removed from her adrenal glands, she began to grow at the rate of a child of 6 months.

In almost all cases, a slowdown follows on the heels of the initial catchup spurt of growth; the children do not "overshoot" the mark. Investigators suspect that some unidentified mechanism attempts to return children to normal patterns of growth even after significant deviations have occurred. This regulative force abides by many of the rules of normal growth.

Usually, the growth of a boy is much more adversely affected than is that of a girl suffering the same medical disorder. Once relieved of the factor that caused the growth lag, however, the boy tends to compensate more quickly than does the girl. For both sexes, the earlier the underlying illness is successfully treated, the more rapid is the rate of catchup growth. By the same token, correction of an illness in later childhood tends to result in a slower rate of catchup growth and is less likely to allow either boy or girl to grow to full potential height.

Weight deficits after illness are usually the most easily overcome. Short stature, the most common disorder of growth, corrects itself less rapidly. Bone maturation, and therefore biological age, is the slowest of the growth parameters to accelerate. For some children, it is almost as if a successfully treated illness signals the body to delay its maturation, and the resultant closure of epiphyses, until the bones have had time to grow to their full length.

Effects of Emotion

The hierarchy of neural and endocrine systems influencing growth appears akin to "the house that Jack built." The pituitary gland is under the control of the hypothalamus, an area at the base of the brain where unconscious activities appear to be initiated. It, in turn, is controlled by higher centers in the nervous system, which themselves are responsive to the cerebral cortex, the portion of the brain presumed responsible for complex and conscious thought. How the cerebral cortex ultimately controls the hypothalamus has always intrigued physicians. To this day, the mechanisms are poorly understood, but they are under increasingly intense investigation because they constitute a physiological means by which basic body processes can be influenced by emotion.

Healthy infants li ing in institutions frequently fail to develop normally. Their failure to thrive has traditionally been attributed to the effects of "emotional deprivation." As a result, social work agencies seek foster home care as an alternative to institutionalization whenever feasible. The theory is that in a private home the child can benefit from the emotional warmth, physical handling, social contact, and sensory stimulation provided by intimate contact with an adequate mother figure. In general, the younger the child, the greater his need for a mother-substitute.

But the home atmosphere some children live in is very deprived. As an example, few physicians can recall a single instance in which an emotionally deprived, inadequately growing child was spontaneously brought for treatment by worried parents. Instead, almost all cases of growth lag are referred by third parties, such as schools, relatives, or other physicians.

Impetus for research on the effect of emotional deprivation on growth and development came in the middle 1960's. Investigators at two General Clinical Research Centers independently reported that a number of children suspected of hypopituitary dwarfism began growing rapidly after they were admitted to the research center and long before institution of HGH therapy.

Many of these children displayed such classical signs of hypopituitary dwarfism as low HGH levels, retarded growth, delayed bone and sexual maturation, and ACTH insufficiency. However, social work investigation revealed a number of unusual factors. The children were exceedingly shy and immature. They came from environments torn by emotional strife, and they were usually rejected by one or both parents. A few patients even showed overt or X-ray evidence of having been physically beaten.

In one of the research center studies, children whose growth retardation was suspected to be caused by emotional deprivation were followed over a 5-year period. For 22 cases in whom no other cause of growth failure could be documented, the median age at admission, was 6 years, but the median bone age was only 3½ years. The growth rate of nine of the patients—those who could be evaluated before hospitalization—was only 1.4 inches a year.

Most of the children in this study were pale and pathologically short. Many also showed significant retardation in social, motor, and intellectual development. They did not play well with siblings or other children. The infants in the group were lethargic, and some had a wide-eyed searching look, known as "radar-like" gaze.

Separation from parents was the principal therapy received by these children. In general, standard pediatric nursing care and normal diets were provided in the hospital. No special calories or protein rations were offered, and medication was generally limited to vitamins and iron.

Despite the paucity of treatment, the majority of the children showed dramatic response. Their rate of growth increased to as much as 6.3 inches a year. In addition, most showed marked physical, emotional, and social improvement by the time they were dismissed from the hospital.

Followup studies revealed that those children subsequently referred to foster care or convalescent homes continued to display significant catch-up growth. On the other hand, the children who returned to their own homes frequently failed to return for followup appointments. Except in those instances in which the home situation had improved, those who did return tended to display a slowdown in growth toward earlier depressed levels.

On the basis of this study, the investigators concluded that these children had normal pituitary glands capable of secreting the HGH required for adequate growth. Their growth retardation appeared clearly due to the influence of emotional deprivation which inhibited, through some unknown mechanism presumably involving nervous pathways between the cerebral cortex and the hypothalamus, sufficient release of the hormone.

Even tiny infants respond adversely to emotional deprivation. Typically, the low birth weight infant spends the early weeks of life in the hygienically controlled but monotonous environment of an isolette. He receives maximum physical care but minimal sensory stimulation. Actual handling of the child is usually confined to times of feeding and diaper changes. One group of General Clinical Research Center investigators hypothesized that the subsequent lag in intellectual and physical growth frequently observed in children of premature or intrauterine retarded birth might be largely due to this emotional isolation imposed upon them in the early weeks of life.

To study this hypothesis, the investigators selected one group of infants within the nursery for special stimulation. In addition to usual nursing care, for 10 days these infants had their backs, necks, and arms rubbed for 5 minutes every hour. Seven to 8 months after discharge from the nursery, the stimulated infants were found to have regained their initial birth weight more speedily and to have developed a more advanced level of activity than had a control group of nonstimulated infants of the same age. These findings tended again to support the theory that emotional deprivation can indeed directly affect rate of development throughout childhood.

Among physicians, however, the existence of a hormonally mediated influence of emotion on human growth processes is not universally accepted. One group of investigators, for example, has reported that growth retardation in emotionally deprived children is more likely caused by inadequate nutrition. This undoubtedly accounted for the growth failure in 11 of 13 emotionally deprived infants who showed significant weight gain in a General Clinical Research Center study in which they were intentionally denied emotional stimulation greater than that which they had received in their homes. It also seems documented by another study in which thin, emotionally deprived infants gained weight adequately in their own homes when fed always in the presence of an observer.

Investigators studying these children believe that only part, or none, of the growth lag seen in emotionally deprived children stems from the hypothalamus. However, all the children reported in these two studies were under 3 years of age and probably were not comparable to the older children described in the preceding discussions. In the latter groups, hypothalamic inhibition of growth hormone release, not nutritional inadequacy, remains the more likely cause of growth failure.

It is true that parents frequently report feeding problems in their emotionally deprived, slow growing children. However, paradoxically, they most often report that their children developed voracious appetites in the first weeks of life that could be satisfied only with great difficulty. As the children grew older and continued to demand excessive quantities of food, the parents frequently made an attempt to limit their food intake. Sometimes, children were locked in their rooms or out of their homes to keep them away from food and drink. The children were said to raid garbage cans and animal dishes and to drink from toilets and mud puddles. They slept poorly and prowled at night, ostensibly looking for something to eat. Stealing and hiding food were common phenomena.

Some researchers have suggested that the contradiction between the "hormone" theory and "nutrition" theory of growth retardation in emotionally deprived children is only apparent. They maintain that there is a hypothalamic influence on growth but that this influence is mediated not through inhibition of HGH secretion but rather through a blockage of intestinal absorption and efficient assimilation of nutrients. Certainly, other disorders of digestion are known to have psychosomatic origin, and this theory would explain the

seeming paradox of poor growth in these children despite excessive food intake.

A study of the effects of anxiety on digestion has been conducted at a General Clinical Research Center. College students were found to require significantly increased protein intake to maintain the stepped-up metabolic activity produced by the stress of preparing for and taking final examinations. This result has been interpreted as lending support to yet another theory—that stress or emotional deprivation may interfere with the action of insulin and, therefore, with the appropriate utilization within the body of sugar and protein.

Thus, the evidence is clear that emotional deprivation can in fact seriously retard growth processes in children. To date, a variety of mechanisms have been proposed to explain how this adverse influence is exerted, and others will likely be advanced in the future. Detailed understanding of how emotions affect growth, however, must in all probability await an even more refined understanding of the process of growth itself.

Adolescence

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The psychology of adolescence has been studied for many years. Only since 1960, however, have medical scientists appreciated that the physiology of adolescence is sufficiently unique to warrant it as a specialized field of study.

Puberty begins when the pituitary gland starts to secrete the gonadotrophins and the gonads, under their influence, begin to release sex hormones. No one knows what triggers the pituitary to begin this secretion or how the time of onset is synchronized with other body processes.

Each individual child, however, appears genetically programed for maturation. Indeed, puberty has now been shown to be the first time in the life of the normal child when heredity overshadows environment in determining how he will grow. Even among abnormally short children, the "least short" are usually the offspring of the tallest parents. Thus, although environmental factors are causing children of the United States today to enter puberty 3 years earlier than they did a century ago, heredity remains the primary reason tall parents beget tall adults, and short parents short adults.

Until the age of 10, boys and girls grow at almost identical rates. Children sharing the same chronological age vary only slightly in size. However, regardless of chronological age, the more advanced the biological age of any child, the closer he is to sexual maturation and the less growth potential he retains. Thus, just as the female comes into life with a more advanced biological age (as measured by bone age), so she enters puberty earlier and emerges from it an adult shorter than her male counterpart.

Puberty usually begins only after at least 85 percent of eventual height has been achieved. Its onset is marked typically by the beginning of breast development in the female and by genital changes in the male. And, although the initial manifestations may be subtle, the growth, the sexual development, and the emotional changes which subsequently characterize puberty can be sufficiently dramatic to make it as difficult a time as any the human must endure.

In both sexes, adrenal androgen appears to be instrumental in initiating the pubescent growth spurt. During the growth spurt, feet and hands first increase in size. The calves and forearms, the hips and chest, and the shoulders then follow, in that order. Because the last to increase is the size of the trunk and chest, the young teenager must almost invariably pass through a transitional stage where his hands and feet are large and ungainly relative to the rest of his body. However, the rate of growth of the trunk in time exceeds that of the lower limbs, and the overall increase in height which occurs during adolescence eventually is derived more from increase in length of the trunk than from growth of the legs.

Although there may be a variation of 3 years between the beginning of the growth spurt in one normal child and another, the typical girl in the United States now begins puberty at the age of 10½. For the next 2½ years, she grows at an average annual rate of 3 inches per year. With the onset of the menstrual cycle, about age 13, the adolescent girl then experiences a rapid decline in growth rate but will continue to grow, at a reduced pace, for another 3 years. By the age of 16, her epiphyses are usually closed, and further increase in height is impossible.

The average adolescent boy, on the other hand, is only beginning his growth spurt at age 13. It will usually be more marked, more intense, and of longer duration than that of the girl. For example, during the next 2½ years, when his height is increasing most rapidly, the adolescent boy usually grows at least 4 inches a year. This is close to the dramatic rate of growth experienced by 2-year-olds. By the time he is 15, he will be eating seven times more protein and 50 percent more calories than he consumed at age 9. Between the ages of 12 and 16, he will almost double in weight.

Although the teenage boy will experience ultimately a decrease in growth rate (and appetite), his decrease is not so precipitous as that of the girl. The epiphyses of his long bones usually do not close, and his increase in height is not over, until he reaches his late teens.

Perhaps as dramatic as the increase in body size which occurs during puberty is the concomitant development of male and female sexual characteristics. The pubescent girl develops rounded contours by accumulating fat on the breasts, hips, and thighs. The boy, on the other hand, becomes during puberty more lean than he will ever be again. The pelvis of the girl enlarges more than do her shoulders; in this way, she is prepared for childbearing. The shoulders and chest of the boy increase more in size than does his pelvis, and his total muscle mass makes tremendous competitive gains.

Bone age is a measure of degree of closure of the epiphyses. Since an adolescent may continue to amass new cells for some time after his epiphyses have closed and his height has stabilized, bone age cannot be used to determine when puberty is complete and adulthood achieved. After full adulthood is reached, however, net increase in total number of body cells does not usually occur; reproduction of cells does continue throughout adult life, but its rate is usually synchronized with cell destruction so that new cells just replace those which are lost. Adulthood, and the end of puberty, therefore, may be defined scientifically as the time a steady state of cell population is finally attained.

Obesity

Many of the medical disorders which disturb the middle-aged and the aged have subtle origin during adolescence. Obesity which develops in childhood tends to continue to plague the individual throughout life. Unfortunately, neither the obese child nor his parents usually become sufficiently concerned about his weight until he is well into puberty—when weight reduction is next to impossible. Since excess weight can generate great anxiety and depression in a teenager, and eventually lead to ill health in adulthood, many clinical investigators in this country are investigating the biochemical reactions and the control mechanisms involved in the storage and breakdown of fats in children. From such studies, hopefully, better methods can be developed to correct obesity in childhood and prevent its becoming a lifelong problem.

Fat infants and plump children may appear delightful to their parents; however, the chances are four out of five that the overweight child will become an overweight teenager who, in turn, will carry his problem throughout adulthood. An estimated one-tenth to one-fourth of the adolescents in this country are overweight.

Adolescent girls negatively relate increasing weight with obesity, while boys tend to view increasing weight positively as a manifestation of growing strength. One recent study of close to 600 high school students showed this disparate, yet mutual, dissatisfaction with weight. Four-fifths of the girls wanted to weigh less; almost all the boys wanted to weigh more. Only the obviously obese among the boys wanted to lose weight.

The young girl emerging into womanhood is frequently torn between social pressures that place a premium on being slender and a maturing metabolism that inexorably deposits fat on her growing body. From a medical standpoint, these fat deposits may fall within the range of healthy female growth. So great are the pressures, however, that previously thin girls may imagine themselves doomed to obesity unless they diet rigorously. These girls constitute a large portion of the American youngsters who, despite access to proper food, exist in a borderline state of nutrition because of ill-advised attempts at weight reduction. Ironically, the diets of overweight girls, whose caloric intake may even be excessive, are also frequently inadequate nutritionally.

To growth researchers, the high correlation between teenage obesity and the incidence of such disorders of the later years as hypertension, heart ailments, diabetes, and respiratory ills makes excess body fat more a medical than an aesthetic concern. For example, in 85 percent of all adult diabetics, obesity preceded the onset of the disease. One theory is that excess body fat in some way produces resistance to the activity of insulin, which in turn causes blood sugar levels to increase. A compensatory increase in secretion of

insulin by the pancreas occurs and continues until the capacity of the pancreas to produce the hormone is exhausted. Then, insulin production falls, and clinical diabetes results. Studies of obese individuals who have lost weight indicate, on the other hand, that once normal weight is regained, elevated insulin levels will often return to normal.

Other studies have indicated that atherosclerosis (the most common form of hardening of the arteries) may begin in the pubescent male. Autopsy studies of boys in the late teen years demonstrate consistently that the fatty arterial plaques which are the constituent beginnings of atherosclerosis can begin during adolescence. As atherosclerosis is the fundamental cause of coronary artery disease, research into its causation and prevention during the adolescent years, and its relation to teenage obesity, may in time have significant influence in reducing the high mortality of American men from heart disease.

Unfortunately, physicians have discovered that for the medically obese boy or girl, puberty may be the most difficult time in life to shed excess pounds. The entire physiology of the adolescent is geared to promote growth, and any attempt to reverse any of its growth parameters may be met with insuperable resistance.

Only temporary decreases in weight have been experienced by obese adolescents in outpatient weight reduction programs. After 1 to 2 years, these teenagers have all reverted to their initial obese status. Greater success has frequently been achieved by teenagers enrolled as inpatients in either hospital or summer camp-based programs. Yet, even for these young people, long-term maintenance of relatively reduced weight has yet to be conclusively demonstrated.

For obese teenagers, therefore, an ounce of prevention is literally worth a pound of cure. The evidence is overwhelming that obesity is best averted, evaluated, or treated as early in life as possible.

The most common, and the simplest, procedure for determining whether an individual is too heavy is to compare his weight with the weight considered normal for one of his height, body frame, age, and sex. However, since total body mass is composed not only of fat but also of bone, muscle, and water, a person may be overweight "by the chart" without being obese. For example, a number of football players were rejected for military duty during World War II because of excess weight. Subsequent analysis revealed that they had little excess fat but were heavier than the normal weight the tables allowed due to their great muscle and bone development.

In recent years, more refined research techniques have been developed to assess with precision the amount of fat in overweight people. They have arisen from the increased interest of physicians in detecting and modifying actual fatness—the one component of overweight that can, and should, be reduced.

One technique relies on the principle of Archimedes. The patient is totally submerged under water, and the volume of water he displaces—which is equal to his body volume—is measured. Total body weight divided by measured body volume equals total body density. Since

the densities of fat, bone, muscle, and water are all different, this calculation of body density enables investigators to determine the proportion of fat in the patient's total weight.

Procedures such as this, however, are too detailed for other than research use. Because half of all pubescent fat is located immediately beneath the skin, researchers have found that the thickness of a fold of skin on the back of the upper arm correlates reasonably well with the amount of body fat present. For example, a 15-year-old girl whose skin fold measures more than an inch is considered obese. Similarly, a 12-year-old boy with a skin fold thickness of at least three-quarters of an inch is also judged obese.

Careful measures of obesity, conducted in a large population of people, coupled with studies of families, documentation of differences in fat accumulation between the sexes, comparisons among racial and ethnic groups, and investigations of identical twins reared together and apart, are yielding impressive evidence that genetic factors may be very important in predisposing certain people to obesity. Too, heredity may also underlie why some underweight individuals do not gain weight despite an obviously excessive caloric intake.

Still unknown, however, is how a genetic predisposition to obesity can be reinforced or overcome by such environmental variables as nutrition, occupation, geography, climate, and emotion. One hypothesis, as noted earlier, is that overnutrition in infancy may stimulate into being a pathologic excess of fat cells which then persist throughout life and tend always to become laden with fat. Another hypothesis, being investigated at a General Clinical Research Center, is that overnutrition may trigger excess production of insulin and HGH in genetically susceptible newborns, which would also encourage excess fat storage. If any such hypothesis can be documented unequivocally, then a significant proportion of adolescent obesity may in time be ascribed more to hormonal or genetic influences than to simple overeating.

Some studies of obese teenage girls have in fact shown their daily caloric intake to be lower than that of lean controls. A possibility, which has not yet been proven, is that these obese girls have hormonal imbalances which in some fashion result in depressed estrogen activity. This, in turn, could allow adrenal androgen, present in normal but limited amount, to exert unopposed its masculinizing effects, with resultant weight gain.

However, neither hormonal dysfunction nor excess caloric intake seems to be the single determinant of obesity. For example, right from birth, obese children are decidedly less active than the nonobese. Movies taken during physical education classes at a swimming pool showed that the fatter teenagers spent 72 percent of their time standing around, whereas their normal weight peers spent 75 percent of their time vigorously engaged in water sports.

The causal relationship between obesity and inactivity is not known. Inactivity may contribute to obesity through reducing the number of food calories which are utilized for energy; alternately, the obese child may be inactive as a result of the heavier weight he must move about. Yet, one fact is certain—every calorie that is spent through increased physical activity is one less calorie that can be stored as fat.

In a recent test, 100 obese adolescent girls were enrolled in a public school physical education program which by design kept them in virtually constant motion for 45 minutes each school day. Also included in the program were nutrition education, psychological support, and encouragement to continue vigorous physical exercise during days off from school.

After 5 months, the girls were compared with a control group of about 70 nonprogram girls. The study group had decreased skin fold thickness an average of 50.5 percent, compared with a decrease of 31.9 percent in the control group. Average body weight decreased 27.7 percent, as against 11.6 percent in nonprogram girls.

As a result of this study, a number of schools are instituting physical education classes specifically designed to help the obese child, who in the past has emerged physiologically untouched (but often scathed psychologically) from traditional physical ed programs that have served only to enhance the skills of the athletically endowed.

Early and Late Puberty

In adolescent boys, the growth spurt occurs at a later age than in adolescent girls. As a result, even a tall boy wants to be taller, and a short boy is fearful he will be short forever. On the other hand, since the girl shoots up much earlier than the boy, she is concerned she will be too tall as an adult and have the same difficulty finding a husband as she does finding a suitably tall dance partner. Since the accepted normal height differential between men and women does not usually result until the years of puberty are ended, increased understanding of the differences between male and female growth rates during adolescence permits physicians today to allay many unwarranted teenage concerns about height. Conversely, researchers are also developing innovative techniques to enable teenagers with medically confirmed growth problems to grow to a height consistent with their peers.

Heredity, not environment, paces the changes of puberty. Since each individual advances from childhood to adulthood at his own genetically determined rate, a teenager cannot validly compare himself with others of the same age. Heredity can either delay biological age and, therefore, growth in the short teenager, or it can usher a tall teenager into puberty at an early age.

Recently developed clinical procedures, including the radioimmunoassay tests, usually reveal that all body systems, in both tall and short teenagers, are working harmoniously. X-rays of wrist epiphyses provide a measure of how far all epiphyses are from closure and, therefore, how much linear growth may yet be achieved.

These procedures reinforce more traditional observations that tall adolescents usually complete growth early, whereas short adolescents continue to grow for long periods. The tall girl will usually grow only a little taller; the height of the short boy can in time exceed that of his tallest friends. Such information can be of great help in reassuring and allaying the fears of the short boy who is afraid he is not growing enough or the tall girl who thinks she will be a giant.

A girl will usually have achieved most of her adult height by the time regular menstrual periods begin. The female hormones, estrogen and progesterone, are responsible for inducing the menarche. Under their influence, growth quickly slows down for the adolescent girl and usually terminates in 2 to 3 years. This influence is the basis for administering these hormones to induce growth retardation in premenstrual girls whose apprehension of excessive adult height has been scientifically confirmed.

Twenty years ago, administration of estrogen was found inadequate to slow down the girl who was growing too tall. In addition, considerable "breakthrough" vaginal bleeding occurred when it alone was given as therapy. In more recent years, however, a research treatment using estrogen in much larger doses and in combination with progesterone has proven very effective, and few adverse effects have been noted.

One General Clinical Research Center confines this research treatment to healthy girls who have inherited the propensity to be over 5 feet 10 inches and in whom the wrist epiphyses are still wide open.

Each day, the patient takes estrogen by mouth. The hormone induces proliferation of the uterine lining, causing it to become progressively soft and thick—just as if the girl were normally ovulating and the uterus were preparing for implantation of a fertilized ovum. To preclude this buildup reaching a point where excessive bleeding might occur, the uterine lining is caused to slough off by injection of a progesterone-like compound the first 5 or 6 days of each month. This duplicates as nearly as possible the cyclic bleeding brought on by the large quantities of progesterone produced physiologically in normally menstruating girls.

In one group of 11 girls, treatment required 8 to 24 months. A decrease in the rate of linear growth was observed in all. Some girls achieved complete growth arrest; others dropped from a growth rate of 4 inches to four-tenths of an inch per year. For patients whose biological age was under 13 when treatment was begun, therapy prevented 2 to 4 inches of predicted growth. Girls whose biological age was over 13 had predicted growth reduced by 1½ to 2½ inches.

Treatment was discontinued when wrist X–rays indicated that growth either had halted or had been reduced to a rate acceptable to the patient. After therapy, menstrual periods resumed a normal pattern. No patient experienced impaired pituitary-ovarian function or blood clots in leg veins—both of which are known, infrequent, but potentially serious complications of this cyclic hormone therapy.

In another similar study, each potentially tall girl received estrogen via a capsule surgically implanted beneath the skin of the abdomen. Each capsule gradually released its hormone into the blood stream and had to be replaced every 6 months. A menstrual-like period was induced by having the patient take a progesterone pill for 5 days each month.

In this study, responsiveness to treatment varied. In about 90 percent of the girls, linear growth halted after 1 to 3 additional inches of growth had occurred. In the remaining 10 percent, less dramatic but still significant growth retardation resulted.

A number of girls from both studies have gone on to get married, enjoy healthy pregnancies, and produce normal babies.

Unlike the girls, adolescent boys are primarily concerned that they may not grow tall enough. Since most boys who are short in the early teenage years will eventually, if slowly, reach normal adult height, growth experts are less likely to intervene in their growth than in the case of girls who are growing too tall. However, if the boy is severely

disturbed by his temporary short stature, some physicians will prescribe male hormones (androgens) to hasten his sexual maturation and, thereby, his growth spurt.

The time at which androgens are utilized to promote growth is important, however, because at the same time that they promote growth, they also begin to stimulate epiphyseal closure. There is a race against time. If sexual maturation proceeds too rapidly, epiphyseal closure may occur prematurely, and the patient may be deprived of the ultimate height he would have reached had his intrinsic chronology of growth been realized without intervention.

In an attempt to avert this danger, some researchers in recent years have begun administering androgens in low doses and on a discontinuous schedule. Usually the patient receives the hormone daily for 1 month and is then taken off all therapy the succeeding month. Bone maturation is evaluated frequently, and the medication is discontinued permanently as soon as the patient's biological age is observed to catch up with his chronological age.

In one study of 67 boys who underwent this intermittent therapy, growth proceeded at the rate of about 3 inches a year so long as all epiphyses remained open. In most cases, ultimate height attained was no more than that predicted; however, most of the boys achieved this height earlier, and a few even grew taller than expected.

The periodic interruption of the medication was felt to lessen the tendency to too-rapid epiphyseal closure. However, the studies are too recent to allow conclusion either that this therapy averts all danger of premature closure or, alternately, that it promotes growth to a height greater than the patient's genetic potential. In fact, one theory as to the efficacy of the treatment is that the small amounts of androgen administered have no direct effect on sexual maturation but that they promote growth only indirectly through stimulation of appetite.

Precocious puberty is the extreme opposite of delayed sexual maturation. In this condition, a girl may develop secondary sexual characteristics before the age of 8, or a boy before he is 10. This clearly can produce severe psychological problems for the affected child.

Of equal importance is the fact that precocious puberty stimulates the adolescent growth spurt to begin prematurely. In normal children, childhood growth is usually complete before the adolescent growth spurt is superimposed; in children with precocious puberty, the growth spurt begins long before the childhood phase of growth is complete. Since sexual maturation tends to promote closure of the epiphyses, this results in epiphyses closed before true potential height is realized and growth of the children into adults noticeably shorter than their contemporaries.

Precocious puberty is rare. Sometimes, it is the first symptom of a cyst or a tumor in the adrenal glands, the sex glands, or the brain. In certain instances, it occurs in families whose members have an inherited tendency to excrete at an early age excessive amounts of adrenal androgen. Many cases have no known origin and may be viewed only as normal puberty occurring at an abnormally early age.

In these latter cases, the continuing development of secondary sexual characteristics can usually be slowed down by the administration of a progesterone-like hormone. Within the past year, researchers have begun to report that this treatment may also slow the accelerated rate of epiphyseal closure. Although these findings remain preliminary, they do indicate that appropriate hormone therapy may eventually allow growth to continue sufficiently long in children with precocious puberty to allow them to attain normal adult height.

Through such studies, scientists are learning how to circumvent the whims of nature that too often impose heavy burdens on young people—particularly during those final years of growth when a young person's perception of himself can be permanently enhanced or flawed. Also, from the information derived, physicians are able to reassure the majority of young people concerned about their growth that, in time, all variations will be spontaneously resolved.

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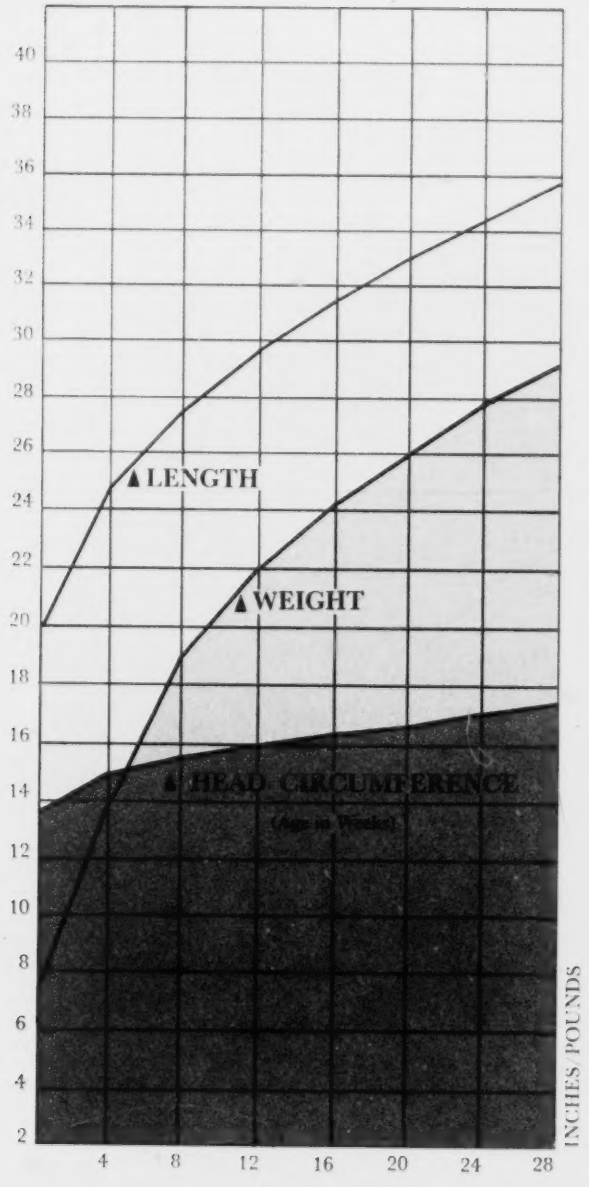
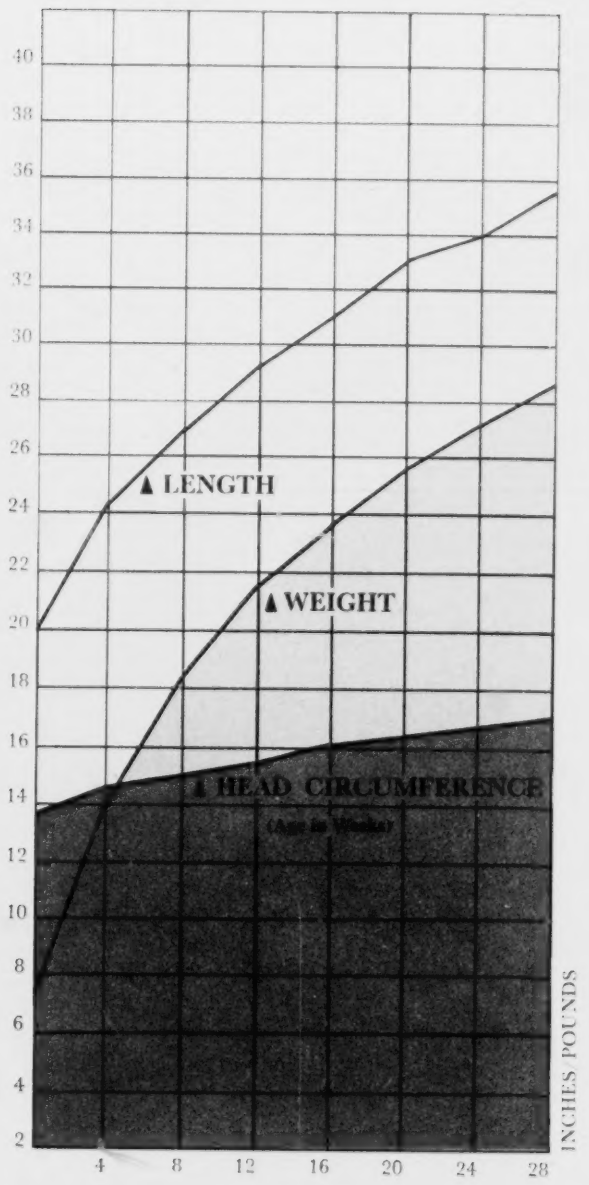
Average Physical Measurements

Black lines indicate 50 percentile.

Infant Boys



Infant Girls



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